Cumulative Network Meta-Analysis and Clinical Practice Guidelines - A Case Study on First-Line Medical Therapies for Primary Open-Angle Glaucoma

by
Benjamin Rouse

A thesis submitted to the Department of Epidemiology of Johns Hopkins Bloomberg School of Public Health in conformity with the requirements for the degree of
Master in Health Science,
Epidemiology,
Clinical Trials and Evidence Synthesis

Baltimore, Maryland
May 2015

Abstract

Background

Clinical practice guidelines are statements of recommendations for patient care. Studies have shown that guideline recommendations do not always depend on evidence from clinical trials or systematic reviews. It is unknown whether no high quality evidence exists, evidence exists but authors were unaware of it, or advanced statistical methods were not available to them to address their questions. Our objective was to compare the guideline recommendations for first-line medical therapy for primary open-angle glaucoma (POAG) from each major update of the American Academy of Ophthalmology's (AAO) Preferred Practice Patterns (PPPs) with the actual evidence base available at the time.

Methods

We identified and extracted recommendations relevant to first-line medical therapy for POAG from each version of the AAO PPP. We searched MEDLINE, EMBASE, and CENTRAL for randomized controlled trials published up to March 2014. We analyzed intraocular pressure (IOP) outcome data as available at the time of each major guideline update. We used network meta-analysis to determine which of all drugs "works best."

Results

We identified 9 versions of AAO's guideline for POAG published between 1989 and 2010. Based on similarity in treatment recommendations or discussion, we grouped these

guidelines into 5 sets: 1989-1992, 1996, 2000-2003; 2005-2006, and 2010. The 2010 guideline recommended prostaglandins as initial treatment, but previous sets presented treatment options without recommending one drug (or class) over another. Based on a series of network meta-analyses of trials published up to around the time of the latest guideline in each set, all drugs are more effective than placebo or no treatment at each time point, but effect size appears to decrease over time. Network meta-analysis indicated that the most effective drug and class (at time point analyzed) were: levobunolol and beta blockers (1991), levobunolol and alpha agonists (1995), travoprost and prostaglandins (2002), bimatoprost and prostaglandins (2004 and 2009).

Conclusions

Network meta-analysis improves our understanding of the comparative effectiveness of multiple interventions. Had network meta-analysis been available, the AAO POAG PPP could have recommended prostaglandins (current first-line treatment) seven years before it actually did. Guideline developers should consider using results from network meta-analyses in forming future recommendations.

Advisor: Tianjing Li, PhD, MD, MHS

Second reader: Roberta W. Scherer, PhD, MS

Acknowledgements

I would like to thank Tianjing Li for serving as my main thesis advisor. I would also like to thank Roberta Scherer for her assistance as a second reader and my academic advisor. I would like to thank Hwanhee Hong, Qiyuan Shi, Lijuan Zeng, Gillian Gresham, Kexin Jin, Cesar Ugarte-Gil, Sueko Ng, and Nan Guo for their help with study screening, data abstraction, and data analysis. Finally, I would like to thank my family and friends for their encouragement throughout the program.

The project was funded by Grant 1 RC1 EY020140 and Grant 1 U01 EY020522, National Eye Institute, National Institutes of Health, United States (PI: Dr. Kay Dickersin).

Table of Contents

1 Introduction

Clinical practice guidelines are statements of recommendations for patient care that are intended to be based on the best available evidence.[1, 2] Historically, guidelines had primarily represented the opinions of individual authors or the consensus of experts.[3] With the advent of evidence-based medicine, however, guidelines have increasingly made use of randomized controlled trials (RCTs) and synthesis of RCTs in the form of systematic reviews and meta-analyses to form the basis of recommendations.[2] Despite the push towards evidence-based guidelines, there may still be many recommendations that are based on lower levels of evidence. Tricoci et al., for example, examined 17 recent cardiovascular guidelines and found that among the 16 guidelines that reported levels of evidence, recommendations were most frequently based on expert opinion, case studies, or standard of care.[4] It is unknown in these cases whether no high quality evidence exists, evidence exists but authors were unaware of it, or advanced statistical methods were not available for them to address their questions.

When quantitatively evaluating the evidence base to make a guideline recommendation, the standard meta-analytic techniques may not always be adequate. A standard meta-analysis can only compare two treatments at a time, and only those treatments that have been compared directly in clinical trials. When developing a guideline for a particular condition, in many cases multiple treatment options must be considered, and direct comparisons may be available only for some pairs of treatments. In these cases, an alternative to the standard meta-analysis may be used, the network meta-analysis. A network meta-analysis looks across the entire network of trials of treatments for a specific condition and uses information from both direct and indirect comparisons

(i.e. using studies comparing treatments A and B and studies comparing B and C to estimate the comparison between A and C) to make inferences about the comparative effectiveness of all treatments in a single analysis.[5,6] Since they enable an "all-way" comparison, network meta-analyses are particularly suited for informing evidence-based guideline recommendations.

Clinical fields which could most benefit from network meta-analysis are those for which a number of treatment options are available. One such area is primary open-angle glaucoma (POAG). POAG is an eye condition in which damage has occurred to the optic nerve and is associated with factors such as high intraocular pressure (IOP), age, and being African American.[7] POAG makes up the majority of glaucoma cases.[8] Since IOP is the only known modifiable risk factor for POAG, treatment efficacy is generally determined by reduction in IOP.[7,9] One of the earliest sets of guidelines that has been influential in the care of POAG is the American Academy of Ophthalmology's (AAO) POAG Preferred Practice Pattern (PPP).[7, 10-17] The first version of this guideline was published in 1989, with major revisions being published approximately every three to five years.

When the AAO PPP guideline was first developed, evidence was gathered based on the guideline panel members' preexisting knowledge; each member submitted what they considered seminal works and these works were distributed among the rest of the panel.[18] In 1996, the panel began using literature searching methods to gather evidence, though details of the search were not reported. The panel also began rating the strength of the evidence in three levels: "I" for evidence from RCTs, "II" for "an appropriately controlled case series and sufficient statistical analysis," and "III" for "expert opinion."[12]

In the 2000 publication, the panel started reporting more details about the literature search, such as databases searched and publication years included.[13] The criteria for strength of the evidence was also revised. "I" represented "strong evidence in support of the statement" based on study design, study populations, general quality, and statistical methods.[13] "II" represented "substantial evidence in support of the statement" based on lacking one or more of the components for level "I" categorization. The definition for "III," similar to before, represented a "consensus of expert opinion."[13] In 2010, the categorizations for strength of evidence were again redefined.[17] "I" was for evidence based on high quality RCTs or meta-analyses. "II" represented evidence from well-designed non-randomized controlled trials, cohort studies, case-control studies, or multiple-time series studies. Support was rated as "III" for evidence from descriptive studies, case reports, or expert committee/organization reports.[17]

By using a cumulative network meta-analysis (i.e. conducting network meta-analysis on a collection of studies published up to a time point), the evidence base for first line medical treatments can be compared with the recommendations for treatment for each major revision in the AAO guideline. Findings from this study will inform guideline developers about the potential benefits of incorporating the results of network meta-analyses to form recommendations in the future. This study is *not* intended as criticism of guideline developers for not using statistical methods that were undeveloped at the time. Rather, we would like to examine what impact such techniques would have had, had they been available at the time.

2 Objective

The objective of this study was to compare the clinical recommendations for first-line medical therapy for POAG from each major update of AAO's POAG PPP with the actual evidence base as determined by network meta-analysis available at the time of each major update.

3 Methods

3.1 Guideline identification and extraction

We identified nine versions of the AAO's POAG PPP from the AAO website (http://www.aao.org/preferred-practice-patterns-publication) from 1989 to 2010, updated about every three to five years. Since only the latest version could be obtained online, we contacted the AAO's librarian who provided the remaining versions.[19] One individual reviewed each version of the guideline, identified sections discussing treatment for POAG, and extracted recommendations on specific drugs or drug classes for initial treatment, references cited for recommendations, and numerical estimates of efficacy or effectiveness (i.e. reduction of IOP) for drugs or drug classes. If a guideline included no specific recommendation for a drug or drug class, we extracted general recommendations for POAG management with medical therapies (e.g. "Medical therapy should be initial treatment for POAG"), as well as discussions about available medical therapies (e.g. "Treatment A is most frequently prescribed as initial treatment"). We considered recommendations evidence-based if they were based on a least one high-quality large RCT or a systematic review. When consecutive guideline versions presented identical recommendations or discussions regarding medical treatment, we grouped them together. Therefore, the nine guidelines were divided into five groups based on their recommendations.

3.2 Systematic review and network meta-analysis

This study was conducted using RCTs identified from an ongoing systematic review.[20] We performed a network meta-analysis for each group of guidelines. Based on the latest guideline in each group, each corresponding network meta-analysis was comprised of all eligible studies published either up to the stopping point for the literature

search reported in the guideline or, if such a point is not reported, a year before that guideline was published (to allow for lag time between publication and inclusion of evidence in guideline). An additional analysis was performed with all studies obtained from the published literature up to 2014.

3.2.1 Eligibility criteria

The eligibility criteria described here are the same as the underlying systematic review, unless otherwise noted.[20] Eligible studies were RCTs with at least 60% of participants having a diagnosis of POAG or ocular hypertension (OHT), as defined by the trial. Trials included in this analysis also had to evaluate first line medical treatments for POAG or OHT, and compared single active treatments with no treatment, placebo, or other single active treatments.

Trials were excluded if less than 10 participants were enrolled per treatment arm or if participants were followed for outcomes less than 28 days after randomization.

For this analysis, we examined mean IOP at 3 months as a continuous variable in units of mmHg as the primary outcome. When a trial measured IOP multiple ways, the priority for selection of IOP measurement was based on the following order: mean diurnal IOP, 24-hour mean IOP, peak IOP, morning IOP, and trough IOP. If a trial did not report IOP values at 3 months, we used data from the closest follow-up time point instead. IOP was selected as the primary outcome based on a preliminary analysis of guidelines indicating that it is the primary efficacy endpoint on which guideline recommendations were made.[7]

3.2.2 Identification of included studies

We searched the Cochrane Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, and EMBASE in November 17, 2009 and the search was

updated in March 11, 2014. Although the Food and Drug Administration (FDA) was searched for additional trials for the underlying systematic review, we did not include these trials in this project because none of the guidelines reported searching the FDA website. The search strategies are available in Appendix 1. Two individuals independently screened titles and abstracts of identified records for potential eligibility. We obtained the full texts for records considered potentially eligible and these articles were then assessed independently for eligibility for the review by two individuals. When feasible, two individuals assessed the non-English language reports for eligibility, otherwise a single individual who was a native or fluent speaker of the language was responsible for assessing eligibility. We resolved discrepancies in classification of eligibility of full text articles through discussion or consultation with a third person.

3.2.3 Data abstraction and management

Two individuals independently abstracted data from eligible trials on the study design, participant and intervention characteristics, outcomes, risk of bias, and quantitative results on treatment effects and safety using electronic forms developed and maintained in the Systematic Review Data Repository (http://srdr.ahrq.gov/).[21,22] We used the Cochrane Risk of Bias Tool to grade each of the following methodological domains at "low" "high" or "unclear" risk of bias: sequence generation and allocation sequence concealment (selection bias), masking of participants and outcome assessors (information bias), trial funding, and author financial relationships.[23] We resolved discrepancies in data abstraction through discussion or consultation with a third person.

3.2.4 Qualitative synthesis

We examined clinical, methodological, and statistical heterogeneity. We investigated clinical heterogeneity in terms of participant characteristics (e.g. age of

participants and baseline IOP) and trial interventions. For methodological heterogeneity, we considered study design and risk of bias.

3.2.5 Quantitative synthesis

Our analysis did not distinguish between drug concentrations; comparisons were based on the active ingredient and class of that ingredient. We first conducted pair-wise meta-analyses for all direct comparisons using random-effects models assuming comparison-specific heterogeneity and a common heterogeneity across all comparisons at both the drug and class level. To assess the statistical heterogeneity, we examined the I^2 and tau^2 values for these models. Pair-wise meta-analyses were conducted in STATA 13®.[24]

Next, we fit Bayesian random-effects network meta-analysis models based on the Lu and Ades approach in WinBUGS 1.4.3.[25-27] This model also accounts for the within-study correlation of multi-arm trials.[25-26] We applied non-informative, yet proper, priors so that the data dominate the posterior distribution. We drew samples of the parameters of interest from the full posterior distribution using Markov Chain Monte Carlo (MCMC) algorithms. We used 2 chains and obtained 50,000 samples (after a 20,000 sample burn-in period). Our approach to model class effect was based on the approach used by Mayo-Wilson et al.[28] In this model, class effect is estimated from the pooled distribution of estimates from individual treatments in that class. This method allows us to use data from all trials for class effect, rather than discarding trials comparing drugs from the same class. We assumed that variance was homogeneous at both the drug and the class level.

3.2.6 Evaluation of network meta-analysis assumptions

A valid network meta-analysis requires the assumption that there are no systematic differences between included comparisons other than the treatments

themselves.[5] We examined this assumption based on the distribution of participant characteristics, interventions, and design characteristics among trials. We further considered the statistical disagreement between direct and indirect comparisons, or inconsistency, present among studies. To assess inconsistency, we used the loop-specific approach with inconsistency models. For the loop-specific approach, each independent closed triangular or quadratic loop (set of three or four treatments connected by direct comparisons) in the network is evaluated for inconsistency and incorporated as separate parameters (i.e. inconsistency factors) in the model.[29-30] This analysis was conducted in STATA 13®.[30-32] When inconsistency was found, we qualitatively investigated trial characteristics such as funding source to determine potential sources of inconsistency.

3.2.7 Measures of relative treatment effect

We examined mean differences in IOP (and 95% confidence intervals or credible intervals) between drug pairs and drug class pairs. We combined both change from baseline values with values at a time point. Due to randomization, it is reasonable to assume that both specific metrics are estimating the same effect.[33] We also determined the probability of rank for each drug or class (i.e. the probability of a drug being the most efficacious treatment, the second most, etc.). We examined the hierarchy of treatment rankings by using the surface below the cumulative ranking curve (SUCRA).[30,34] A SUCRA value (or percentage) gives the probability that a treatment is among the best treatments, with a value of 1 (or 100%) meaning that a treatment is certain to be the best and 0 (or 0%) meaning that a treatment is certain to be the worst. Rankings based on SUCRA values are considered to better take into account uncertainty in estimated treatment effects than general ranking probabilities.[30,34]

3.3 Guideline and network meta-analysis comparison

We compared information extracted from each guideline group to the results of the corresponding network meta-analysis to assess frequency of matching of recommended drugs or drug classes and efficacy estimates in the guideline with the most efficacious drug or drug class from the network meta-analysis (based on SUCRA values).

4 Results

4.1 Guideline identification and extraction

We identified 9 version of the AAO's POAG PPP: 1989, 1990, 1992, 1996, 2000, 2003, 2005, 2006, and 2010.[7,10-17] Based on recommendations and level of discussion of POAG medical therapies, we grouped the guidelines together into 5 different sets: 1991-1992, 1996, 2000-2003, 2005-2006, and 2010 (Table 1). Of these guideline sets, only 2010 made recommendations on first-line medical therapy. Based on a meta-analysis of 11 glaucoma trials, the 2010 guideline stated that "Prostaglandin analogs are the most effective drugs at lowering IOP and can be considered as initial medical therapy." However, no other guideline set made any specific recommendations with regard to which drug or class of drug is most efficacious; guideline statements have focused on describing available options, therapies most often used as first-line treatment, or general guidance for treatment. For example, the 2005-2006 guideline set stated that "In many instances, topical medications constitute effective initial therapy" instead of making a specific recommendation. Of the guideline sets, the 2005-2006 and 2010 sets reported stopping points for literature searches. Therefore, the time points for network meta-analysis were 1991, 1995, 2002, 2004, and 2009, with an additional one comprising all collected data up to 2014.

4.2 Network meta-analysis

4.2.1 Search results and general study characteristics

We identified 10,936 unique records from the search. For this analysis, a total of 105 RCTs from the published literature met our eligibility criteria (Figure 1; references for these trials are available in Appendix II). The first trial was published in 1983 and the latest trial in 2013. The network included 18 trials (1,161 participants) by 1991, 29 trials

(2,641 participants) by 1995, 66 trials (9,446 participants) by 2002, 76 trials (10,717 participants) by 2004, and 91 trials (13,870 participants) by 2009. As of 2014, there are a total 16,898 participants in the network of 105 trials. Detailed characteristics of individual trials are included in Appendix III.

The study characteristics described include all trials published by the network meta-analysis time point. Sample size of studies appears to be smaller in earlier years than later ones. In 1991, the median size of trials was 69 participants (interquartile range (IQR): 28 to 85). This increased to 72 participants (IQR: 42 to 137) by 1995, and 95 participants (IQR: 45 to 177) by 2002. Afterwards, study sample size does not appear to change substantially, with a median of 91 participants (IQR: 43 to 195) by 2004 and 90 participants (IQR: 47 to 213) by 2009. As of 2014, the median sample size of trials is 97 (IQR: 49 to 218). The smallest trial (17 participants) was published in 1985 and the largest (976 participants) in 2005.

The proportion of trials reported to be multicenter also appears to be smaller in earlier years: 39% of trials were reported to be multicenter in 1991, 55% in 1995, 70% in 2002, 64% in 2004, 61% in 2009, and 65% as of 2014. Reported regions of participant recruitment (in 1991 and 2014 respectively) are North America (28% to 37%), Latin America (0% to 3%), Europe (0% to 17%), Africa (0% to 1%), Asia (6% to 16%), Oceania (0% to 2%) (trials could recruit participants from more than one region; remaining trials did not report region).

The length of trials is generally longer for earlier studies. Median trial length was 6 months (IQR: 3 to 15) in 1991 and 6 months (IQR: 3 to 12) in 1995. For all network meta-analysis time points after 1995, median length was 3 months (IQR: 3 to 12).

4.2.2 Risk of bias

At all network meta-analysis time points, the risk of bias of included studies was generally unclear to high, although the proportion of trials with low risk of bias appears to be higher at later time points (Figure 2a-f; Appendix IV). The proportion of studies with low risk of bias from sequence generation ranges from 11% in 1991 (89% unclear) to 43% in 2014 (57% unclear). 17% of studies published by 1991 were rated to have a low risk of bias for allocation concealment (83% unclear) while 27% published by 2014 were (73% unclear). We rated the risk of bias from masking of participants to be low for 33% of studies up to 1991 (11 % high; 56% unclear) and 39% of studies up to 2014 (21% high; 40% unclear). 17% of studies to 1991 (83% unclear) were rated to have a low risk of bias due to masking of IOP assessor, and 22% of studies were rated low up to 2014 (10% high; 69% unclear). In trials published up to 1991, only 33% reported funding, of which 100% had industry funding and 33% were funded by government (a trial could report more than one funding source). By 2014, 59% reported funding, of which 92% reported industry funding and 13% reported government funding. Of trials published by 1991, 33% reported on author financial conflicts of interest, of which 100% reported conflicts of interest for at least one author. By 2014, 52% of trials reported on conflicts of interests, of which 67% reported existing conflict of interest for least one author.

4.2.3 Interventions

Included trials studied 13 active interventions from 4 different classes, as well as placebo/vehicle/no treatment (Figure 3a-f). The active interventions were apraclonidine and brimonidine (alpha-2 adrenergic agonists); betaxolol, carteolol, levobunolol, and timolol (beta blockers); brinzolamide and dorzolamide (carbonic anhydrase inhibitors);

and bimatoprost, latanoprost, travoprost, tafluprost, and unoprostone (prostaglandin analogs). By 1991, three active drugs (betaxolol, levobunolol, and timolol) from one class (beta blockers) and placebo were studied in RCTs. In 1995, the network of studies included an additional five drugs (apraclonidine, carteolol, dorzolamide, latanoprost, and unoprostone), and at least one drug from each class was included. The network expanded to 11 active drugs in 2002 with brimonidine, brinzolamide, and travoprost. By 2004, 12 of the active drugs were in the network and no additional drugs were added in 2009. As of 2014, one more drug, tafluprost, has been studied in the network.

4.2.4 Network meta-analysis outcomes

Network meta-analysis indicates that all drugs (and classes) are superior to placebo in lowering 3-month IOP at all network meta-analysis time points (Table 2a-l; Figure 4a-b). Results are reported in terms of mean IOP (in mmHg) and 95% credible interval. The drugs and classes with the largest effect on IOP reduction compared with placebo at each time point are: 1991: levobunolol 4.53 (3.31 to 5.79), beta blockers 4.01 (0.48 to 7.43); 1995: apraclonidine 5.63 (2.56 to 8.64), alpha agonists 5.64 (1.73 to 9.50); 2002: travoprost 6.02 (4.64 to 7.38), prostaglandins 4.97 (3.29 to 6.65); 2004: bimatoprost 5.87 (4.67 to 7.06), prostaglandins 4.75 (3.11 to 6.44); 2009 bimatoprost 5.87 (4.96 to 6.77), prostaglandins 4.58 (2.94 to 6.24); 2014: bimatoprost 5.55 (4.80 to 6.31), prostaglandins 4.38 (3.03 to 5.75). Point estimates for drug and class effects appear to diminish over time (Figure 4a-b).

Many direct comparisons between drugs, such as latanoprost vs placebo, are missing even by 2014 and for the direct comparisons that exist, there are often only one or two trials (Appendix V). The class effect estimates from direct comparison differ greatly from those obtained from combining direct and indirect comparisons. For

example, by 2014 only two trials have directly compared prostaglandins with placebo and the pooled estimate is not significantly superior to placebo.

Ranking probabilities are consistent with the network meta-analysis effect estimates (Figure 5a-l). By 2014, for example, bimatoprost had a 93.4% chance of being the most efficacious drug in terms of effect on 3-month IOP, 6.1% chance of being the second best, and 0.5% chance of being the third best, while as a class, prostaglandins had 73.9% chance of being the best, 19.8% of being the second best, and 5.4% of being the third best. Ranking based on cumulative ranking probabilities from SUCRA plots are also generally consistent with effect estimates (Figure 6a-b). The only time at which the highest cumulative rank did not match with treatment effect was in 1995, in which apraclonidine was had the highest mean effect but levobunolol had the highest cumulative ranking. By 2004, rankings generally stabilized for both drugs and classes. Sometimes, when two drugs were included at the same time point, they crossed in cumulative rank at subsequent points (Figure 6a-b). For example, from 2002 to 2009, brimonidine was ranked higher than timolol, but by 2014, their positions switched.

4.2.5 Inconsistency

By 2014, the loop-specific approach to inconsistency indicated evidence of inconsistency in 5 of 34 triangular loops (15%). We could not find any qualitative reasons to explain inconsistency among studies included in the inconsistent loops.

4.3 Guideline and network meta-analysis comparison

A summary of the comparison between guidelines recommendations and network meta-analytic findings is given in Table 3. Based on network-meta-analysis, it would have been possible to make treatment recommendations for all guideline sets, such as that beta blockers were superior to placebo/no treatment based on RCT data available by

1991. The only time evidence from network meta-analysis with the guideline recommendation is in 2010, as both indicate that the prostaglandin class should be considered the first-line treatment in terms of efficacy.

5 Discussion

AAO's POAG PPP did not make specific recommendations for first-line treatment until 2010. However, based on network meta-analysis, there was sufficient evidence to conclude that medical treatments superior to placebo existed by 1991. The 2010 recommendation is supported by the network meta-analysis results. The ranking of classes based on the effect sizes given in the 2010 guidelines are also consistent with our findings. Prostaglandins have the largest effect, beta blockers and alpha agonists are next and are very close in effect, and carbonic anhydrase inhibitors are the least effective. In both the 2010 guideline and the corresponding network meta-analaysis, even though prostaglandins are considered the most efficacious class, the magnitude of IOP reduction does not really appear to differ substantially between classes.

The AAO's POAG PPPs do not give recommendations at the drug level. This may be because the guideline producers did not want to appear to favor a particular drug manufacturer, since some glaucoma drugs, such as bimatoprost, are still under patent. Our results indicate that drugs within a class generally have similar effects on IOP. The most notable exception is unoprostone, which was the least effective drug at all time points since 2004 despite the high ranking of all other prostaglandins. With unoprostone, there is uncertainty whether it should be classified as a prostaglandin analogue or not.[35-36] Despite being derived from prostaglandin F(2α) like the other prostaglandin drugs, pharmacological studies have suggested that unoprostone has a distinct mechanism of action compared to the other prostaglandins, and therefore it may not be appropriate to group it with these other drugs.[35-36] If unoprostone is really part of a separate drug class, it would explain the great disparity in IOP effect, as well as indicate that our findings for

prostaglandin effect may underestimate the true class effect. Other exceptions are betaxolol, which has a lower effect than the other beta blockers, and the two alpha agonists, apraclonidine and brimonidine, which start off with different effectiveness profiles but appear to get closer in effect size and ranking over time. Since within-class treatments are generally similar, it is appropriate for guidelines to make recommendations at the class level for POAG treatments.

One interesting finding from the cumulative network meta-analysis is that, as can be seen in Figure 4, there appears to be a consistent pattern that the effect size for all glaucoma treatments diminishes over time. Despite this, all treatments are superior to placebo at all network meta-analysis time points. This result is consistent with findings by Gehr et al., who, in a meta-regression, determined that the effect size for both timolol and latanoprost decreased over time.[37] One potential explanation for this finding is due to small-study effects; the tendency for smaller studies to produce larger treatment effects than larger studies due to factors like publication bias or poorer methodological quality of smaller studies.[38] Earlier studies in the network were smaller, but even when median study size stops increasing in 2002, treatment effect size still diminishes. Another possibility is that in earlier studies, participants had less severe disease or more easily controlled IOP. After drugs became established in RCTs, people entering trials may be those with more severe disease or whose IOP was not controlled on initial therapy. In Gehr et al.'s study, it was found that a significant relationship existed between baseline IOP values and treatment effect over time in the case of timolol.[37] We will further explore the data to try and determine the decrease in effect size over time.

The AAO PPPs used IOP as the major determinant in forming treatment recommendations and so did our analysis, yet it is widely understood that IOP is a surrogate outcome for visual function.[39] Visual field is considered an outcome more clinically relevant to visual function, but requires longer follow-up time than IOP to accurately assess changes (generally years).[39] Based on our included studies, median follow-up time in POAG trials is 3 months by 2014, preventing meaningful assessment of visual field. Some studies, such as the recent UK Glaucoma Treatment Study, which was conducted to assess whether latanoprost preserves visual field in addition to reducing IOP, have indicated that IOP and visual field are associated.[40] On the other hand, trials such as the Low-Pressure Glaucoma Treatment Study, which found that participants assigned to brimonidine had better preserved visual field than those on timolol despite mean IOP being similar in both groups, have suggested that depending on IOP is questionable.[39,41] An additional concern is that even if IOP is demonstrated to be a reliable predictor for visual field for treatments in one class, different classes may affect visual field progression differently despite having a similar ocular hypotensive effect.[39] In terms of the guidelines, the AAO POAG PPPs have considered the evidence associating IOP with risk of visual field progression to be sufficient that IOP is an acceptable outcome for trials since 1996.[7,13-17]

Cumulative pair-wise meta-analysis has demonstrated the importance of using meta-analysis instead of just looking at individual RCTs to inform treatment recommendations. A cumulative meta-analysis by Antman et al. showed that sufficient RCT evidence existed to confirm that thrombolytic therapy significantly reduced the risk of death from myocardial infarction by 1973, but that it took 13 years (by which the

number of RCTs had increased from 10 to 43) for the therapy to be recommended for routine practice by expert reviewers.[42]

Network meta-analysis has begun to be recognized as a useful tool for guideline developers. The Endocrine Society commissioned a network meta-analysis to be conducted to inform recommendations for its 2012 clinical practice guideline for osteoporosis in men.[43-44] The National Institute for Health and Clinical Excellence (NICE) in Europe also conducted its own network meta-analysis for making recommendations on neuropathic pain treatments.[45]

By extending the principles of cumulative meta-analysis to network meta-analysis, we have provided evidence that network meta-analysis can benefit clinical guideline developers. If network meta-analysis results had been available to developers, the POAG PPP could have made recommendations for initial medical treatment at each major update. Furthermore, the current first-line treatment, prostaglandins, could have been recommended as early as the 2003 update, seven years earlier than when prostaglandins were recommended. Another strength of our analysis is that we were able to estimate class effect without discarding trials comparing drugs from the same class.

Our findings regarding network meta-analysis and guideline comparisons may not be applicable to other clinical fields or even other glaucoma guidelines such as those developed by the National Institute for Health and Clinical Excellence,[9] since we only examined a single set of guidelines. The cultures of other clinical fields or different glaucoma guideline groups may lead them to have different approaches to making treatment recommendations (e.g. drug level instead of class level) or in their use of evidence as the basis for recommendations.

Conclusion

We identified 5 sets of guidelines from AAO's POAG PPPs with major revisions in terms of medical treatment recommendations or discussions of therapies. Treatment recommendations were only made in the final set. Using cumulative network meta-analysis, we were able to determine the best drug and class at the time of each major revision based on RCT evidence available at the time. Both the final guideline and the corresponding network meta-analysis indicate that prostaglandins should be considered first-line treatment in terms of IOP reduction. Other findings from the network meta-analysis are that the effect size for all drugs and classes appears to decrease over time, but all were significantly better than placebo at all time points. Network meta-analysis results have the potential to help clinical guideline developers make evidence-based recommendations.

6 References

1. Institute of Medicine. Clinical Practice Guidelines We Can Trust. 2011
2. Institute of Medicine. Knowing What Works in Healthcare: Roadmap for the Nation. 2008
3. Eddy DM. Evidence-based medicine: a unified approach. *Health Aff (Millwood)*. 2005;24(1):9–17.
4. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA*. 2009;301(8):831–41.
5. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods*. 2012;3(2):80–97.
6. Cipriani. 2013. Conceptual and technical challenges in network meta-analysis.
7. American Academy of Ophthalmology. Primary Open-Angle Glaucoma Preferred Practice Patterns. San Francisco: American Academy of Ophthalmology; 2010
8. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90:262-7.
9. National Institute for Health and Care Excellence. NICE guidelines. Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension. 2009.
10. American Academy of Ophthalmology. Primary Open-Angle Glaucoma Preferred Practice Patterns. San Francisco: American Academy of Ophthalmology; 1989
11. American Academy of Ophthalmology. Primary Open-Angle Glaucoma Preferred Practice Patterns. San Francisco: American Academy of Ophthalmology; 1990
12. American Academy of Ophthalmology. Primary Open-Angle Glaucoma Preferred Practice Patterns. San Francisco: American Academy of Ophthalmology; 1992
13. American Academy of Ophthalmology. Primary Open-Angle Glaucoma Preferred Practice Patterns. San Francisco: American Academy of Ophthalmology; 1996

14. American Academy of Ophthalmology. Primary Open-Angle Glaucoma Preferred Practice Patterns. San Francisco: American Academy of Ophthalmology; 2000

15. American Academy of Ophthalmology. Primary Open-Angle Glaucoma Preferred Practice Patterns. San Francisco: American Academy of Ophthalmology; 2003

16. American Academy of Ophthalmology. Primary Open-Angle Glaucoma Preferred Practice Patterns. San Francisco: American Academy of Ophthalmology; 2005

17. American Academy of Ophthalmology. Primary Open-Angle Glaucoma Preferred Practice Patterns. San Francisco: American Academy of Ophthalmology; 2006

18. Sommer A, Weiner JP, Gamble L. Developing specialty-wide standards of practice: the experience of ophthalmology. *QRB Qual Rev Bull*. 1990;16(2):65–70.

19. "The American Academy of Ophthalmology." *American Academy of Ophthalmology*. Accessed 21 Aug. 2014. http://www.aao.org/

20. Li T, Lindsey K, Rouse B, et al. Comparative Effectiveness of First-line Medications for Patients with Primary Open Angle Glaucoma or Ocular Hypertension – A Systematic Review and Network Meta-analysis (in process)

21. Ip S, Hadar N, Keefe S, Parkin C, Iovin R, Balk EM, Lau J. A Web-based archive of systematic review data. *Syst Rev*. 2012;1(1):15.

22. Li T, Vedula SS, Hadar N, Parkin C, Lau J, Dickersin K. Innovations in data collection, management, and archiving for systematic reviews. *Ann Intern Med*. 2015;162(4):287-94.

23. Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

24. StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.

25. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23(20):3105-3124.

26. Lu G, Ades a. E. Assessing Evidence Inconsistency in Mixed Treatment Comparisons. *J Am Stat Assoc*. 2006;101(474):447–459.

27. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS— a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput*. 2000; 10: 325–37.

28. Mayo-Wilson E, Dias S, Mavranezouli I, et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. *The Lancet Psychiatry*. 2014;1(5):368–376.

29. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making*. 2013;33(5):641-656.

30. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One*. 2013;8(10):e76654.

31. White IR. Multivariate random-effects meta-regression : Updates to mvmeta. *Stata J.* 2011;11(2):255-270.

32. White IR, Barrett JK, Jackson D, Higgins JPT. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods*. 2012;3(2):111–125.

33. Deeks JJ, Higgins JPT, and Altman DG on behalf of the Cochrane Statistical Methods Group. Chapter 9.4.5.2 Meta-analysis of change scores. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org; accessed on April 29, 2015

34. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol*. 2011;64(2):163–71.

35. Harms N V, Toris CB. Current status of unoprostone for the management of glaucoma and the future of its use in the treatment of retinal disease. *Expert Opin Pharmacother*. 2013;14(1):105-113.

36. Fung DS, T WJ. An evidence-based review of unoprostone for glaucoma : place in therapy. *Clin Ophthalmol*. 2014;8:543-554.

37. Gehr BT, Weiss C, Porzsolt F. The fading of reported effectiveness. A meta-analysis of randomised controlled trials. *BMC Med Res Methodol*. 2006;6:25.

38. Sterne J AC, Gavaghan D, Egger M. Publication and related bias in meta-analysis: Power of statistical tests and prevalence in the literature. *J Clin Epidemiol*. 2000;53(11):1119-1129.

39. Medeiros FA. Biomarkers and surrogate endpoints in glaucoma clinical trials. *Br J Ophthalmol*. 2014:1–5.

40. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2014:1295-1304.

41. Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S. A randomized trial of brimonidine versus timolol in preserving visual function: Results from the low-pressure glaucoma treatment study. *Am J Ophthalmol*. 2011;151(4):671-681.

42. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. *JAMA*. 1992;268(2):240-248

43. Watts NB, Adler R a, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(6):1802-1822.

44. Murad MH, Drake MT, Mullan RJ, et al. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *J Clin Endocrinol Metab*. 2012;97(6):1871-1880.

45. National Institute for Health and Care Excellence. NICE guidelines. Neuropathic pain – pharmacological management: The pharmacological management of neuropathic pain in adults in non-specialist settings. 2013.

7 Tables

7.1 Table 1 Recommendations from AAO POAG PPPs

Guideline sets	Recommendation for or discussion of POAG first-line medical treatment	Recommendation basis[a]	Numerical estimates of therapy efficacy	Additional comments
1989, 1990, 1992	"[We] do not have results from any large, randomized clinical trials of medical therapy for glaucoma"	NR	NR	Guidelines discuss general principles for medical treatment, but make no recommendations for first-line treatment Commonly used medical treatments and dosages are also discussed, but no efficacy estimates are given. Classes discussed are miotics, epinephrine drugs, beta blockers, and carbonic anhydrase inhibitors.
1996	"IOP can be lowered by medical treatment"; "In most instances, topical medications are initial therapy."	NR; Consensus of expert opinion	Carbonic anhydrase inhibitors: 20-30% IOP reduction	No reference is given for the the estimated efficacy of carbonic anhydrase inhibitors. Drug classes commonly used for POAG mentioned, but in less detail than 1989-1992 set. Classes include miotics, epinephrine compounds, alpha agonists, prostaglandins, beta blockers, and carbonic anhydrase inhibitors. Cannibinoids are also discussed as an option
2000, 2003	"IOP can be lowered by medical treatment"; "In most instances, topical medications are initial therapy."	NR; Consensus of expert opinion	NR	Estimated effect of carbonic anhydrase inhibitors included in 1996 guideline and discussion of cannibinoids removed.Otherwise, discussion of POAG therapies similar to 1996 guideline.
2005, 2006	"In many instances, topical medications constitute effective initial therapy"	NR	NR	Available treatment options discussed. Options include prostaglandins, beta-blockers, alpha agaonists, carbonic anhydrase inhibitors, and parasympathomimetics (miotics).
2010	"Prostaglandin analogs are the most effective drugs at lowering IOP and can be considered as initial medical therapy unless other considerations such as cost, side effects, intolerance, or patient refusal preclude this."	Meta-analysis[b]	Prostaglandin analogs: 25-30% IOP reduction; Beta blockers: 20-25% IOP reduction; Alpha-adrenergic agonists: 20-25% IOP reduction; Parasympathomimetic agents: 20-25% IOP reduction; Carbonic anhydrase inhibitors: 15-20% IOP reduction	First guideline in series to make specific recommendation regarding first-line medical treatment. No specific drugs (e.g. bimatoprost, latanoprost) mentioned; recommendation only at class level Data for efficacy estimates taken from European Glaucoma Society guidelines[c]

NR: Not reported

[a] As reported in guideline

[b] Stewart WC, Konstas AG, Nelson LA, Kruft B. Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines. Ophthalmology 2008;115:1117-22.

[c] European Glaucoma Society. Terminology and Guidelines for Glaucoma. 3rd ed. Savona, Italy:Editrice Dogma S.r.l.; 2008:127

7.2 Table 2 Summary estimates for intraocular pressure (mmHg) at 3 months derived from network meta-analysis

7.2.1 Table 2a Network meta-analysis IOP estimates for drugs from studies published by 1991

Placebo	Apraclonidine	Brimonidine	Betaxolol	Carteolol	Levobunolol	Timolol	Brinzolamide	Dorzolamide	Bimatoprost	Latanoprost	Travoprost	Tafluprost	Unoprostone
-	-												
NA	-	-											
(NA;NA)	-												
3.27	-	-	-										
(1.97;4.69)	-	-											
-	-	-	-	-									
-	-	-	-										
4.53	-	-	1.26	-	-								
(3.31;5.79)	-	-	(-0.02;2.50)	-									
4.26	-	-	0.99	-	-0.27	-							
(3.19;5.34)	-	-	(-0.08;2.05)	-	(-1.05;0.44)								
-	-	-		-	-	-	-						
-	-	-	-	-	-	-							
-	-	-	-	-	-	-	-	-					
-	-	-	-	-	-	-	-						
-	-	-	-	-	-	-	-	-	-				
-	-	-	-	-	-	-	-	-					
-	-	-	-	-	-	-	-	-	-	-			
-	-	-	-	-	-	-	-	-	-				
-	-	-	-	-	-	-	-	-	-	-	-		
-	-	-	-	-	-	-	-	-	-	-			
-	-	-	-	-	-	-	-	-	-	-	-	-	
-	-	-	-	-	-	-	-	-	-	-	-		
-	-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-	

7.2.2 Table 2b Network meta-analysis IOP estimates for drugs from studies published by 1995

Placebo												
5.63 (2.56;8.64)	Apraclonidine											
-	-	Brimonidine										
-	-											
3.61 (2.43;4.82)	-2.02 (-5.02;1.02)	-	Betaxolol									
3.75 (2.02;5.49)	-1.89 (-5.12;1.4)	-	0.13 (-1.53;1.78)	Carteolol								
5.36 (4.30;6.41)	-0.27 (-3.23;2.70)	-	1.75 (0.66;2.81)	1.62 (0.08;3.17)	Levobunolol							
4.83 (3.88;5.78)	-0.80 (-3.67;2.07)	-	1.22 (0.28;2.13)	1.09 (-0.43;2.6)	-0.53 (-1.24;0.19)	Timolol						
-	-	-	-	-	-	-	Brinzolamide					
-	-	-	-	-	-	-						
4.03 (2.54;5.5)	-1.60 (-4.76;1.55)	-	0.42 (-1.07;1.85)	0.29 (-1.70;2.24)	-1.33 (-2.77;0.11)	-0.80 (-2.12;0.49)	-	Dorzolamide				
-	-	-	-	-	-	-	-	-	Bimatoprost			
-	-	-	-	-	-	-	-					
5.49 (3.40;7.54)	-0.15 (-3.55;3.27)	-	1.87 (-0.23;3.93)	1.74 (-0.67;4.13)	0.12 (-1.85;2.09)	0.66 (-1.19;2.5)	-	1.45 (-0.78;3.71)	-	Latanoprost		
-	-	-	-	-	-	-	-	-	-	-	Travoprost	
-	-	-	-	-	-	-	-	-	-	-		
-	-	-	-	-	-	-	-	-	-	-	-	Tafluprost
-	-	-	-	-	-	-	-	-	-	-	-	
4.88 (2.83;6.97)	-0.75 (-4.12;2.7)	-	1.27 (-0.77;3.32)	1.14 (-1.21;3.5)	-0.48 (-2.44;1.53)	0.05 (-1.77;1.92)	-	0.85 (-1.36;3.15)	-	-0.61 (-2.75;1.52)	-	-	Unoprostone

7.2.3 Table 2c Network meta-analysis IOP estimates for drugs from studies published by 2002

Placebo													
3.48 (1.89;5.07)	Apraclonidine												
4.58 (3.58;5.55)	1.10 (-0.45;2.64)	Brimonidine											
3.13 (2.24;4.02)	-0.35 (-1.89;1.18)	-1.45 (-2.34;-0.53)	Betaxolol										
4.05 (2.91;5.17)	0.57 (-1.11;2.24)	-0.53 (-1.67;0.62)	0.92 (-0.13;1.96)	Carteolol									
4.94 (4.07;5.82)	1.47 (-0.08;3.01)	0.37 (-0.56;1.3)	1.81 (1;2.63)	0.90 (-0.09;1.89)	Levobunolol								
4.33 (3.58;5.07)	0.85 (-0.58;2.27)	-0.25 (-0.98;0.5)	1.20 (0.57;1.82)	0.28 (-0.59;1.16)	-0.61 (-1.21;-0.02)	Timolol							
2.80 (1.54;4.04)	-0.68 (-2.51;1.13)	-1.78 (-3.13;-0.41)	-0.33 (-1.6;0.93)	-1.25 (-2.69;0.2)	-2.14 (-3.44;-0.86)	-1.53 (-2.69;-0.36)	Brinzolamide						
3.26 (2.38;4.13)	-0.21 (-1.79;1.35)	-1.31 (-2.27;-0.36)	0.14 (-0.69;0.94)	-0.78 (-1.88;0.3)	-1.68 (-2.55;-0.81)	-1.06 (-1.73;-0.4)	0.46 (-0.63;1.55)	Dorzolamide					
-	-	-	-	-	-	-	-	-	Bimatoprost				
-	-	-	-	-	-	-	-	-					
5.72 (4.84;6.6)	2.25 (0.73;3.76)	1.15 (0.38;1.92)	2.59 (1.82;3.37)	1.67 (0.67;2.7)	0.78 (0;1.56)	1.39 (0.87;1.92)	2.92 (1.67;4.18)	2.46 (1.67;3.26)	-	Latanoprost			
6.02 (4.64;7.38)	2.55 (0.67;4.41)	1.45 (0.12;2.78)	2.90 (1.56;4.21)	1.98 (0.54;3.43)	1.08 (-0.21;2.37)	1.70 (0.55;2.85)	3.22 (1.58;4.87)	2.76 (1.43;4.07)	-	0.30 (-0.87;1.48)	Travoprost		
-	-	-	-	-	-	-	-	-	-	-	-	Tafluprost	
-	-	-	-	-	-	-	-	-	-	-	-		
3.16 (2.1;4.23)	-0.32 (-1.9;1.26)	-1.42 (-2.41;-0.37)	0.03 (-0.88;0.96)	-0.89 (-2.05;0.3)	-1.79 (-2.77;-0.77)	-1.17 (-1.95;-0.35)	0.36 (-1.01;1.75)	-0.11 (-1.08;0.91)	-	-2.56 (-3.29;-1.81)	-2.87 (-4.21;-1.5)	-	Unoprostone
									-			-	

7.2.4 Table 2d Network meta-analysis IOP estimates for drugs from studies published by 2004

Placebo												
2.98 (1.43;4.56)	Apraclonidine											
4.20 (3.3;5.09)	1.22 (-0.34;2.78)	Brimonidine										
2.76 (2.02;3.52)	-0.22 (-1.76;1.32)	-1.44 (-2.27;-0.57)	Betaxolol									
3.63 (2.55;4.71)	0.65 (-1.05;2.34)	-0.57 (-1.68;0.54)	0.87 (-0.18;1.91)	Carteolol								
4.59 (3.79;5.4)	1.61 (0.04;3.17)	0.40 (-0.49;1.3)	1.83 (1.04;2.61)	0.96 (-0.03;1.97)	Levobunolol							
3.90 (3.24;4.55)	0.92 (-0.53;2.36)	-0.3 (-0.99;0.41)	1.14 (0.54;1.72)	0.27 (-0.6;1.15)	-0.69 (-1.28;-0.11)	Timolol						
2.69 (1.51;3.89)	-0.29 (-2.11;1.51)	-1.51 (-2.79;-0.21)	-0.07 (-1.27;1.13)	-0.94 (-2.34;0.49)	-1.90 (-3.13;-0.66)	-1.21 (-2.31;-0.09)	Brinzolamide					
2.96 (2.15;3.77)	-0.02 (-1.61;1.55)	-1.24 (-2.15;-0.32)	0.2 (-0.59;0.96)	-0.67 (-1.75;0.42)	-1.64 (-2.49;-0.78)	-0.94 (-1.58;-0.29)	0.27 (-0.8;1.32)	Dorzolamide				
5.87 (4.67;7.06)	2.89 (1.09;4.67)	1.67 (0.49;2.84)	3.10 (1.92;4.26)	2.24 (0.9;3.58)	1.27 (0.11;2.43)	1.97 (0.95;2.97)	3.18 (1.66;4.66)	2.91 (1.71;4.09)	Bimatoprost			
5.24 (4.49;5.99)	2.26 (0.75;3.76)	1.04 (0.36;1.74)	2.48 (1.78;3.16)	1.61 (0.63;2.59)	0.65 (-0.09;1.38)	1.34 (0.89;1.8)	2.55 (1.37;3.72)	2.28 (1.53;3.02)	-0.63 (-1.63;0.39)	Latanoprost		
5.44 (4.34;6.54)	2.46 (0.74;4.16)	1.24 (0.17;2.33)	2.68 (1.61;3.74)	1.81 (0.57;3.07)	0.85 (-0.22;1.91)	1.54 (0.64;2.44)	2.75 (1.32;4.16)	2.48 (1.4;3.57)	-0.42 (-1.57;0.72)	0.20 (-0.68;1.09)	Travoprost	
-	-	-	-	-	-	-	-	-	-	-	-	Tafluprost
-	-	-	-	-	-	-	-	-	-	-	-	
2.45 (1.55;3.36)	-0.53 (-2.13;1.04)	-1.75 (-2.67;-0.78)	-0.32 (-1.17;0.54)	-1.18 (-2.3;-0.03)	-2.15 (-3.08;-1.2)	-1.45 (-2.18;-0.7)	-0.24 (-1.55;1.05)	-0.51 (-1.44;0.44)	-3.42 (-4.63;-2.18)	-2.79 (-3.49;-2.07)	-2.99 (-4.1;-1.87)	- -

Unoprostone

7.2.5 Table 2e Network meta-analysis IOP estimates for drugs from studies published by 2009

Placebo													
2.88 (1.26;4.52)	Apraclonidine												
3.84 (2.95;4.73)	0.96 (-0.64;2.56)	Brimonidine											
2.51 (1.75;3.27)	-0.38 (-1.97;1.21)	-1.33 (-2.16;-0.49)	Betaxolol										
3.53 (2.42;4.66)	0.65 (-1.1;2.39)	-0.30 (-1.44;0.84)	1.03 (-0.04;2.1)	Carteolol									
4.57 (3.75;5.4)	1.69 (0.08;3.32)	0.74 (-0.16;1.64)	2.07 (1.27;2.87)	1.04 (0.01;2.08)	Levobunolol								
3.80 (3.14;4.47)	0.92 (-0.58;2.41)	-0.04 (-0.71;0.65)	1.29 (0.7;1.89)	0.27 (-0.65;1.18)	-0.77 (-1.39;-0.16)	Timolol							
2.51 (1.42;3.61)	-0.38 (-2.15;1.41)	-1.33 (-2.5;-0.15)	0.00 (-1.09;1.11)	-1.03 (-2.36;0.31)	-2.07 (-3.21;-0.93)	-1.29 (-2.27;-0.31)	Brinzolamide						
2.65 (1.88;3.42)	-0.23 (-1.87;1.39)	-1.19 (-2.08;-0.29)	0.14 (-0.63;0.91)	-0.89 (-2;0.23)	-1.92 (-2.79;-1.07)	-1.15 (-1.8;-0.5)	0.14 (-0.85;1.14)	Dorzolamide					
5.87 (4.96;6.77)	2.99 (1.36;4.63)	2.03 (1.16;2.91)	3.36 (2.49;4.22)	2.33 (1.21;3.45)	1.29 (0.41;2.18)	2.07 (1.42;2.72)	3.36 (2.19;4.53)	3.22 (2.32;4.12)	Bimatoprost				
5.05 (4.3;5.81)	2.17 (0.63;3.72)	1.22 (0.56;1.88)	2.55 (1.86;3.22)	1.52 (0.51;2.53)	0.48 (-0.27;1.22)	1.25 (0.81;1.7)	2.55 (1.49;3.6)	2.41 (1.66;3.15)	-0.81 (-1.47;-0.15)	Latanoprost			
5.10 (4.18;6.03)	2.22 (0.59;3.85)	1.26 (0.39;2.15)	2.60 (1.72;3.47)	1.57 (0.44;2.7)	0.53 (-0.37;1.42)	1.30 (0.63;1.96)	2.60 (1.42;3.77)	2.45 (1.54;3.37)	-0.77 (-1.51;-0.02)	0.05 (-0.63;0.72)	Travoprost		
-	-	-	-	-	-	-	-	-	-	-	-	Tafluprost	
-	-	-	-	-	-	-	-	-	-	-	-	-	Unoprostone
2.31 (1.38;3.25)	-0.57 (-2.23;1.07)	-1.53 (-2.48;-0.56)	-0.20 (-1.07;0.68)	-1.22 (-2.41;-0.04)	-2.26 (-3.24;-1.28)	-1.49 (-2.26;-0.72)	-0.20 (-1.4;1.02)	-0.34 (-1.29;0.63)	-3.56 (-4.51;-2.58)	-2.75 (-3.48;-2)	-2.79 (-3.75;-1.83)	-	-

7.2.6 Table 2f Network meta-analysis IOP estimates for drugs from studies published by 2014

Placebo													
2.73 (1.19;4.25)	Apraclonidine												
3.58 (2.84;4.33)	0.86 (-0.62;2.35)	Brimonidine											
2.40 (1.7;3.11)	-0.32 (-1.84;1.2)	-1.18 (-1.92;-0.45)	Betaxolol										
3.42 (2.39;4.45)	0.70 (-0.97;2.36)	-0.16 (-1.19;0.86)	1.02 (0.01;2.04)	Carteolol									
4.46 (3.7;5.23)	1.73 (0.2;3.27)	0.87 (0.09;1.67)	2.06 (1.3;2.82)	1.04 (0.05;2.03)	Levobunolol								
3.68 (3.1;4.27)	0.96 (-0.45;2.38)	0.10 (-0.46;0.66)	1.28 (0.72;1.84)	0.26 (-0.6;1.13)	-0.78 (-1.37;-0.19)	Timolol							
2.44 (1.61;3.29)	-0.28 (-1.85;1.3)	-1.14 (-1.93;-0.34)	0.04 (-0.83;0.93)	-0.98 (-2.11;0.16)	-2.01 (-2.94;-1.09)	-1.24 (-1.98;-0.5)	Brinzolamide						
2.56 (1.87;3.26)	-0.17 (-1.7;1.37)	-1.03 (-1.79;-0.25)	0.15 (-0.57;0.88)	-0.87 (-1.91;0.19)	-1.90 (-2.71;-1.09)	-1.13 (-1.73;-0.53)	0.11 (-0.7;0.92)	Dorzolamide					
5.55 (4.8;6.31)	2.83 (1.3;4.35)	1.97 (1.24;2.7)	3.15 (2.38;3.91)	2.13 (1.11;3.15)	1.09 (0.3;1.87)	-1.90 (-2.71;-1.09)	3.11 (2.2;4)	3.00 (2.2;3.78)	Bimatoprost				
4.86 (4.21;5.52)	2.14 (0.68;3.6)	1.28 (0.71;1.85)	2.46 (1.83;3.09)	1.44 (0.49;2.39)	0.40 (-0.29;1.09)	1.18 (0.79;1.56)	2.42 (1.61;3.21)	2.3 (1.63;2.97)	-0.69 (-1.24;-0.14)	Latanoprost			
4.94 (4.15;5.72)	2.21 (0.69;3.75)	1.35 (0.61;2.1)	2.53 (1.75;3.31)	1.51 (0.48;2.55)	0.48 (-0.33;1.28)	1.25 (0.69;1.82)	2.49 (1.58;3.4)	2.38 (1.57;3.18)	-0.62 (-1.18;-0.05)	0.08 (-0.49;0.63)	Travoprost		
4.39 (3.03;5.79)	1.67 (-0.2;3.56)	0.81 (-0.54;2.17)	1.99 (0.62;3.38)	0.97 (-0.55;2.51)	-0.07 (-1.45;1.33)	0.71 (-0.54;1.98)	1.95 (0.51;3.41)	1.84 (0.46;3.23)	-1.16 (-2.49;0.18)	-0.47 (-1.74;0.82)	-0.54 (-1.88;0.8)	Tafluprost	
2.17 (1.32;3.04)	-0.56 (-2.12;0.99)	-1.42 (-2.27;-0.55)	-0.24 (-1.06;0.59)	-1.26 (-2.37;-0.13)	-2.29 (-3.21;-1.36)	-1.52 (-2.23;-0.79)	-0.28 (-1.28;0.72)	-0.39 (-1.28;0.51)	-3.39 (-4.24;-2.52)	-2.69 (-3.38;-2)	-2.77 (-3.63;-1.9)	-2.23 (-3.65;-0.84)	Unoprostone

7.2.7 Table 2g Network meta-analysis IOP estimates for classes from studies published by 1991

Placebo				
-	Alpha agonists			
-				
4.01	-	Beta blockers		
(0.48;7.43)	-			
-	-	-	Carbonic anhydrase inhibitors	
-	-	-		
-	-	-	-	Prostaglandins
-	-	-	-	

7.2.8 Table 2h Network meta-analysis IOP estimates for classes from studies published by 1995

Placebo				
5.64 (1.73;9.5)	Alpha agonists			
4.39 (2.8;5.96)	-1.24 (-5.26;2.75)	Beta blockers		
4.03 (1.18;6.89)	-1.6 (-6.26;3.04)	-0.36 (-3.4;2.69)	Carbonic anhydrase inhibitors	
5.18 (2.72;7.65)	-0.46 (-4.86;3.96)	0.79 (-1.83;3.44)	1.15 (-2.42;4.76)	Prostaglandins

7.2.9 Table 2i Network meta-analysis IOP estimates for classes from studies published by 2002

Placebo				
4.03 (1.97;6.05)	Alpha agonists			
4.11 (2.66;5.53)	0.08 (-2.2;2.41)	Beta blockers		
3.03 (1.04;4.99)	-1.00 (-3.69;1.73)	-1.08 (-3.37;1.18)	Carbonic anhydrase inhibitors	
4.97 (3.29;6.65)	0.94 (-1.47;3.43)	0.86 (-1.12;2.86)	1.94 (-0.46;4.41)	Prostaglandins

7.2.10 Table 2j Network meta-analysis IOP estimates for classes from studies published by 2004

Placebo				
3.59 (1.27;5.9)	Alpha agonists			
3.72 (2.11;5.35)	0.13 (-2.55;2.84)	Beta blockers		
2.83 (0.59;5.09)	-0.76 (-3.88;2.38)	-0.89 (-3.59;1.77)	Carbonic anhydrase inhibitors	
4.75 (3.11;6.44)	1.16 (-1.5;3.9)	1.03 (-1.13;3.23)	1.92 (-0.76;4.64)	Prostaglandins

7.2.11 Table 2k Network meta-analysis IOP estimates for classes from studies published by 2009

Placebo				
3.36 (0.99;5.7)	Alpha agonists			
3.60 (1.98;5.23)	0.24 (-2.48;2.99)	Beta blockers		
2.58 (0.34;4.8)	-0.78 (-3.89;2.38)	-1.02 (-3.67;1.65)	Carbonic anhydrase inhibitors	
4.58 (2.94;6.24)	1.23 (-1.46;3.98)	0.99 (-1.15;3.14)	2.00 (-0.65;4.67)	Prostaglandins

7.2.11 Table 2l Network meta-analysis IOP estimates for classes from studies published by 2014

Placebo				
3.15 (1.04;5.21)	Alpha agonists			
3.49 (2.04;4.94)	0.35 (-2.06;2.82)	Beta blockers		
2.49 (0.53;4.45)	-0.65 (-3.42;2.15)	-1.00 (-3.36;1.33)	Carbonic anhydrase inhibitors	
4.38 (3.03;5.75)	1.23 (-1.09;3.62)	0.89 (-0.94;2.72)	1.89 (-0.39;4.18)	Prostaglandins

Color coding: drug class
Mean difference < 0 favors the drug in the column
Mean difference > 0 favors the drug in the row
Reported numbers are calculated by column - row under the Lu and Ades homogeneous random effects model assuming consistency
Reported posterior means and 95% Bayesian credible intervals

Grey	Placebo/vehicle/no treatment
Orange	Alpha-2 adrenergic agonist
Green	Beta-blocker
Red	Carbonic anhydrase inhibitor
Blue	Prostaglandin analog

7.3 Table 3. Guideline and network meta-analysis comparison

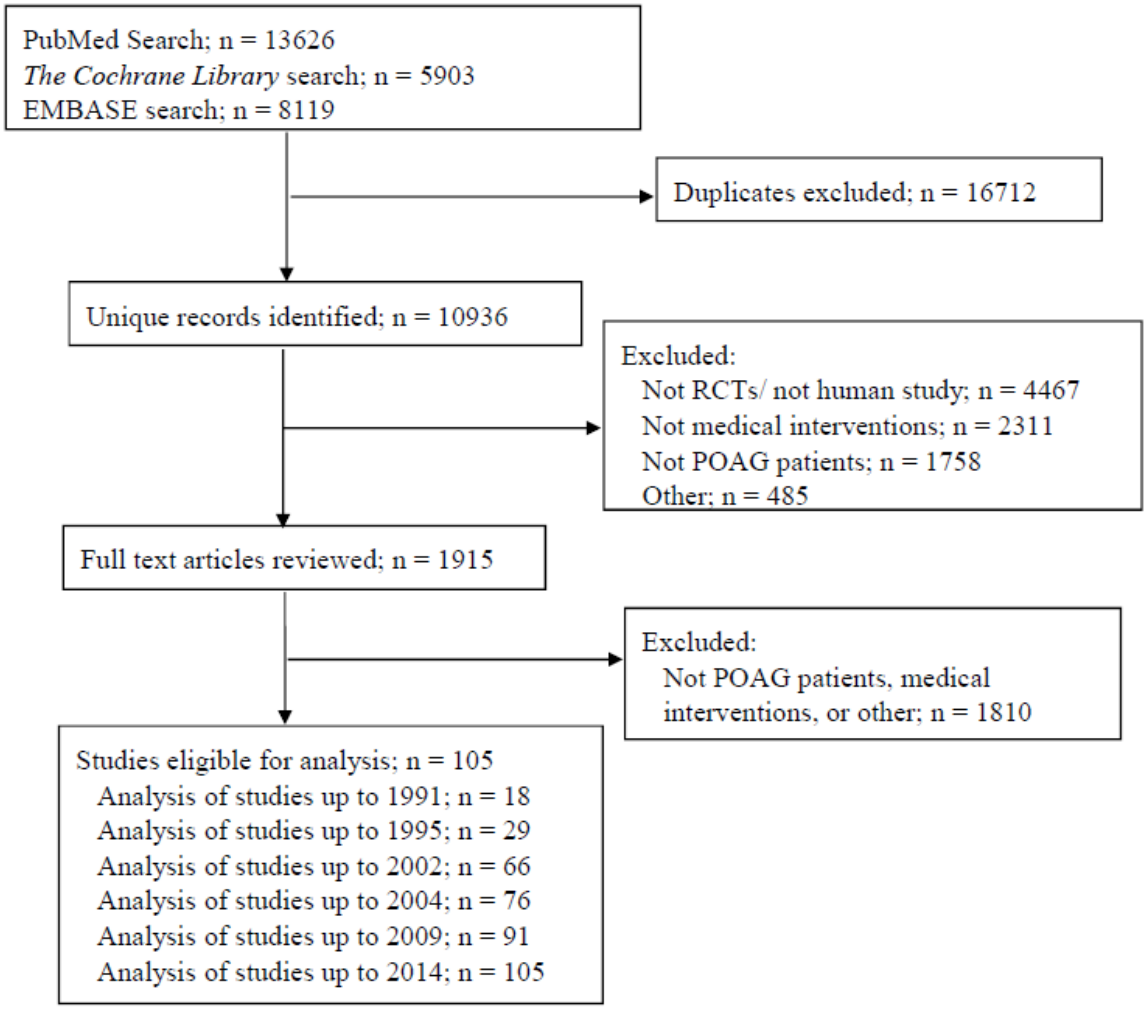
Guideline sets	Guideline first-line therapy recommendation (estimated IOP reduction)	Highest NMA cumulative ranking probability (IOP reduction mmHg)[a]	
		Drug	Class
1989, 1990, 1992	NR	Levobunolol (4.53)	Beta blockers (4.01)
1996	NR	Levobunolol (5.36)	Alpha agonists (5.64)
2000, 2003	NR	Travoprost (6.02)	Prostaglandins (4.97)
2005, 2006	NR	Bimatoprost (5.87)	Prostaglandins (4.75)
2010	Prostaglandins (25-30%)	Bimatoprost (5.87)	Prostaglandins (4.58)

NR: No recommendation

[a]IOP reduction relative to placebo

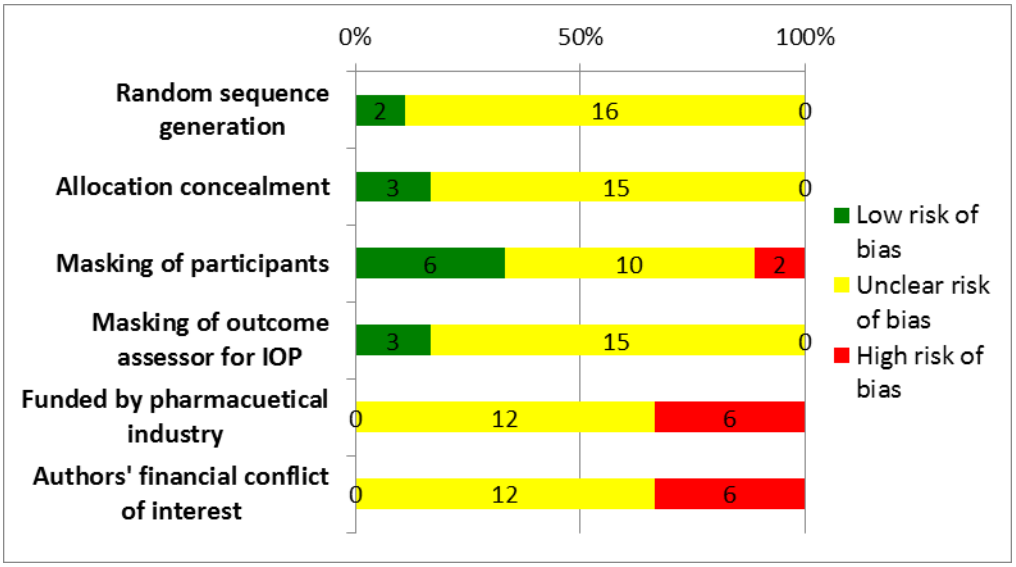
8 Figures

8.1 Figure 1 Selection of studies

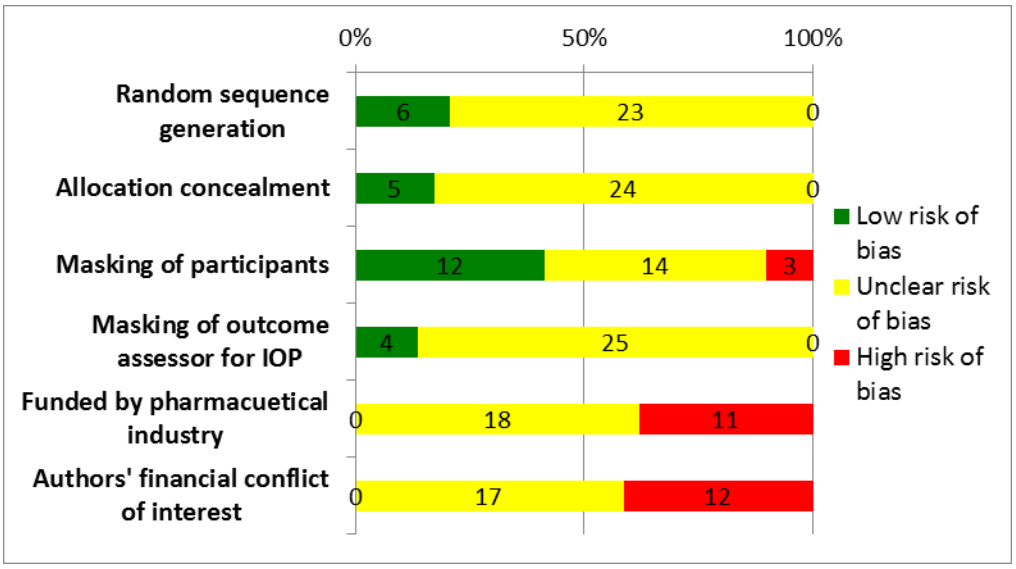


8.2 Figure 2 Risk of bias figure

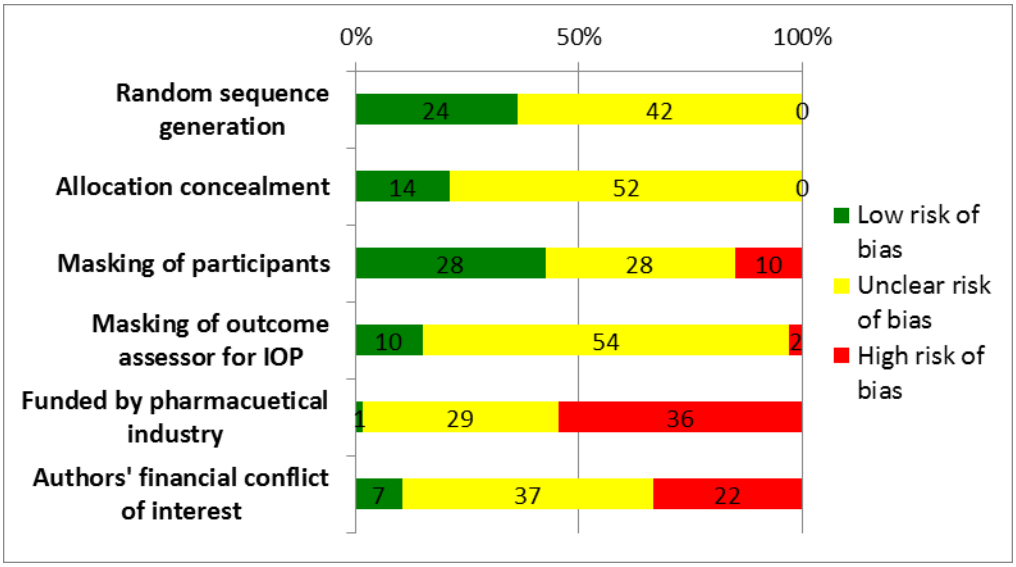
8.2.1 Figure 2a Risk of bias figure for studies published up to 1991



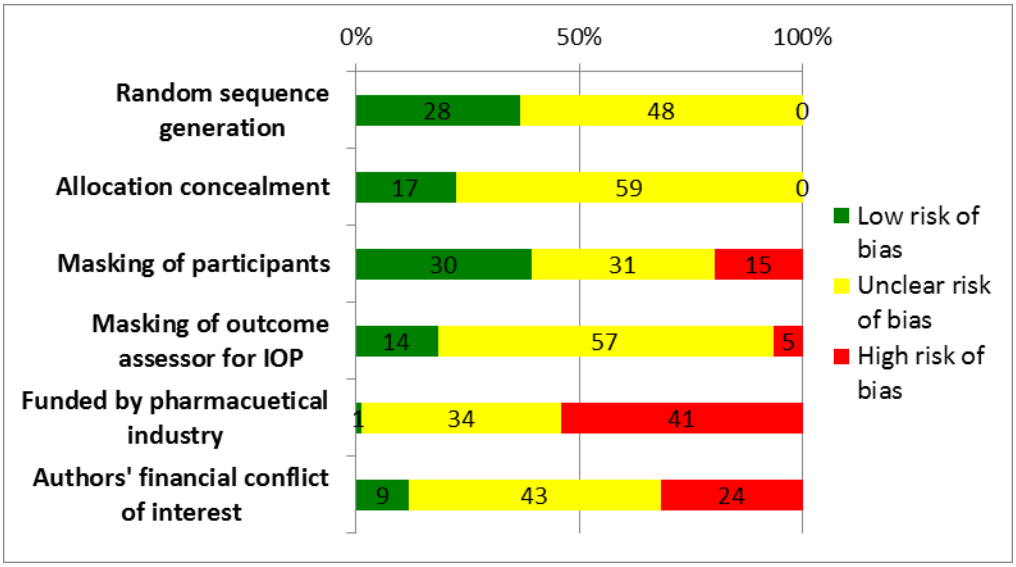
8.2.2 Figure 2b Risk of bias figure for studies published up to 1995



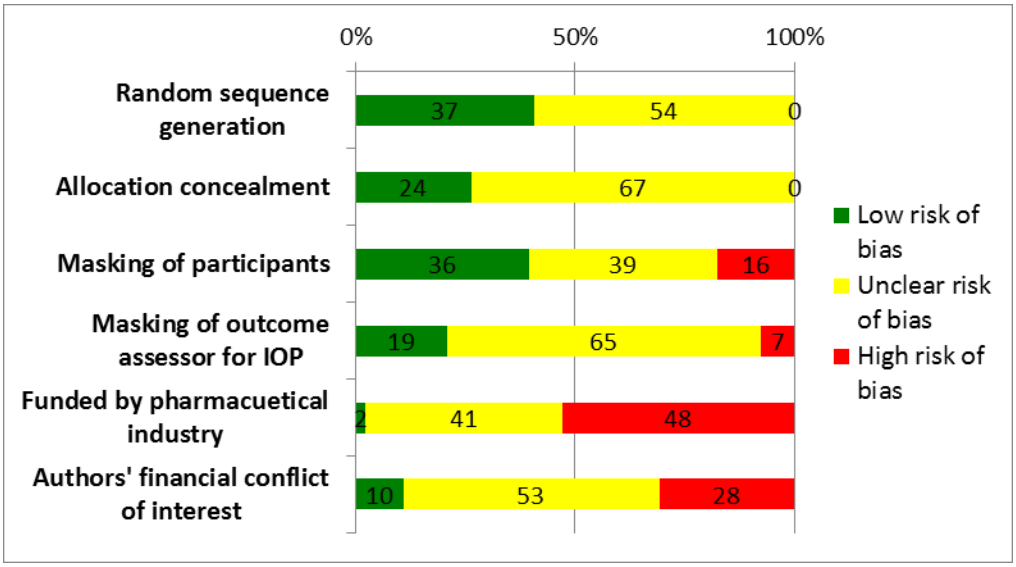
8.2.3 Figure 2c Risk of bias figure for studies published up to 2002



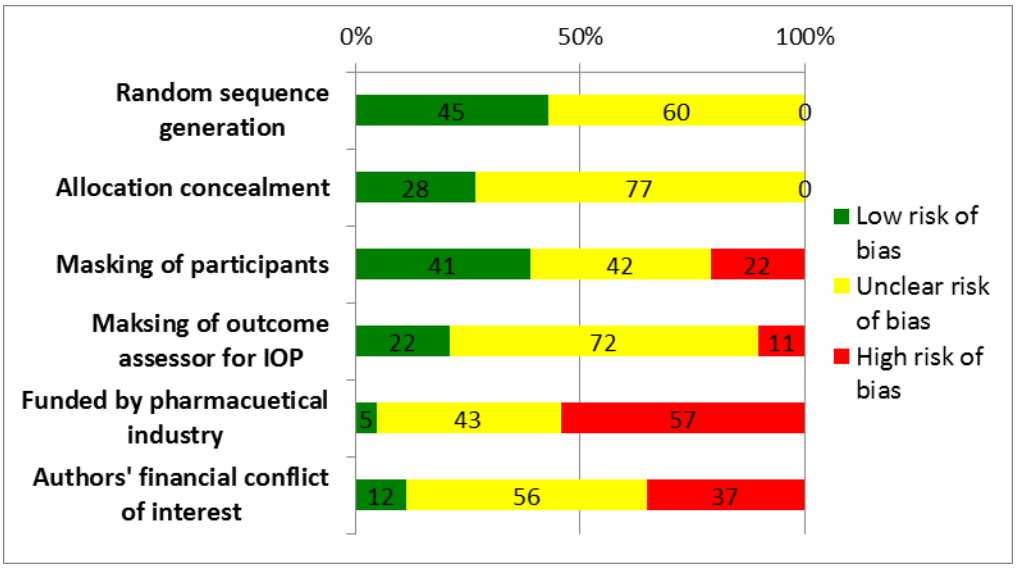
8.2.4 Figure 2d Risk of bias figure for studies published up to 2004



8.2.5 Figure 2e Risk of bias figure for studies published up to 2009

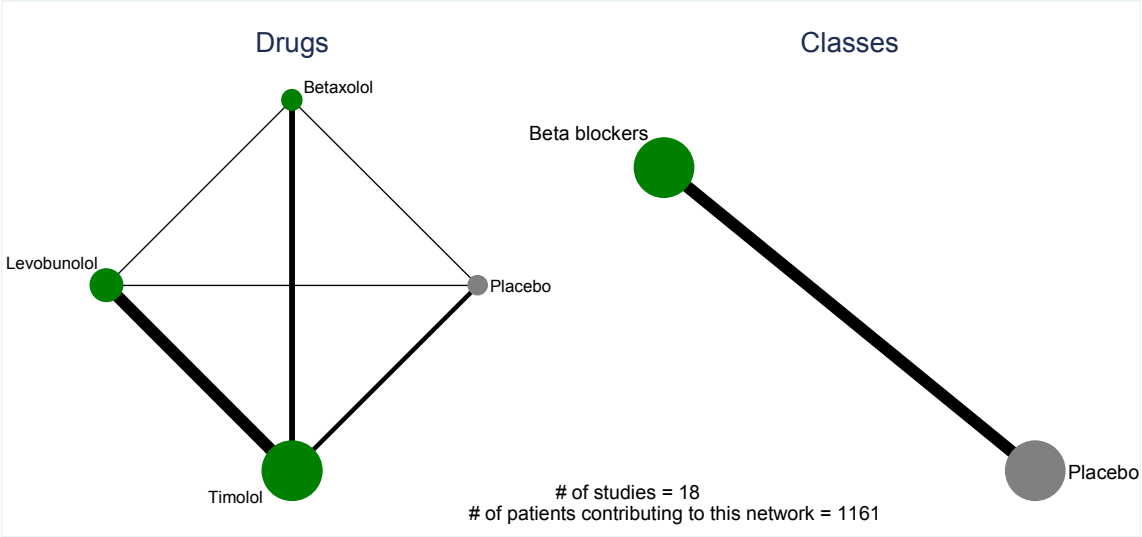


8.2.6 Figure 2f Risk of bias figure for studies published up to 2014

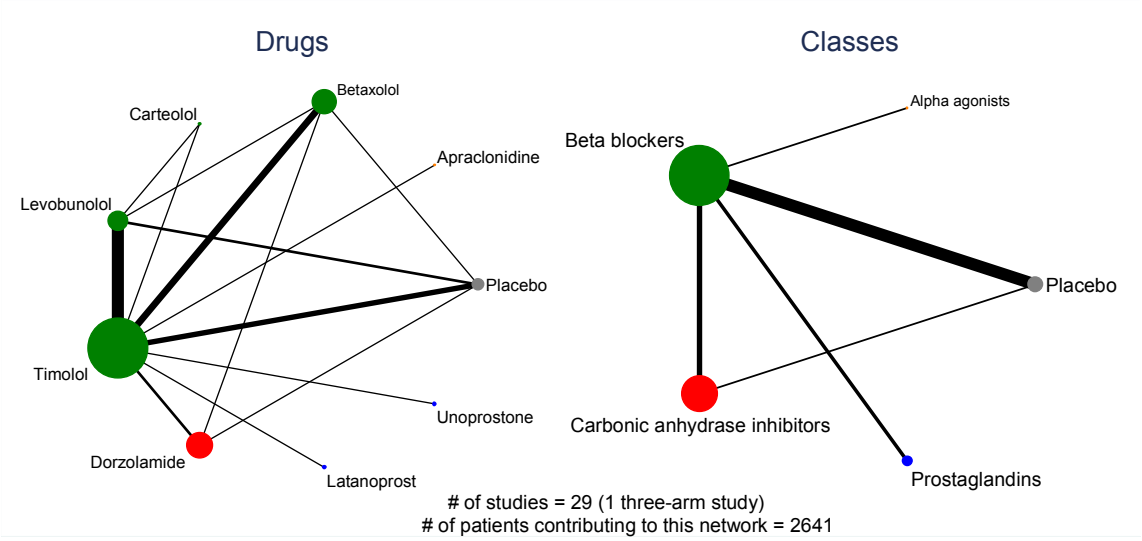


8.3 Figure 3 Network graphs

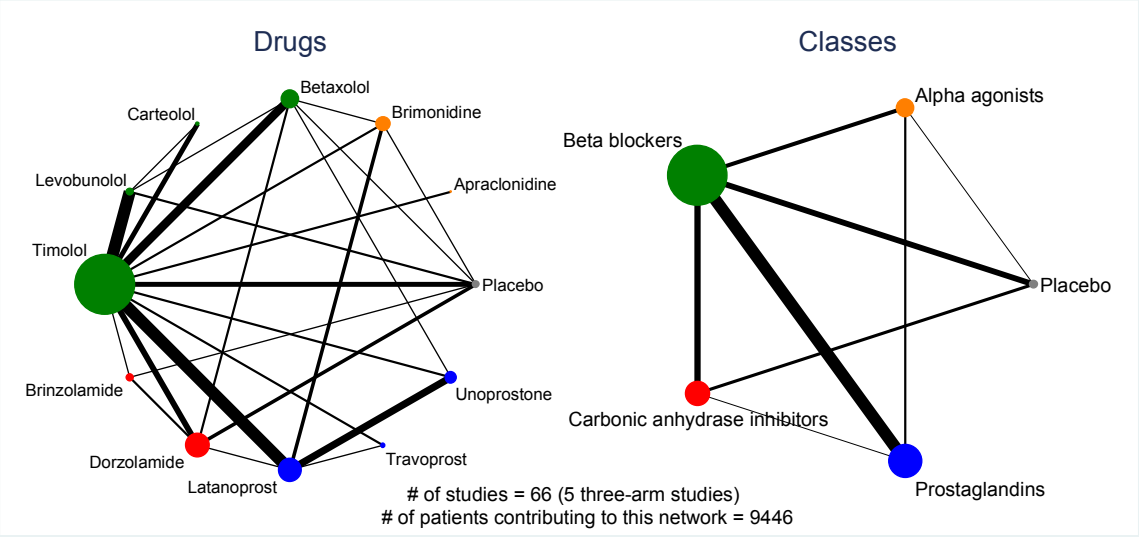
8.3.1 Figure 3a Network graph for studies published up to 1991



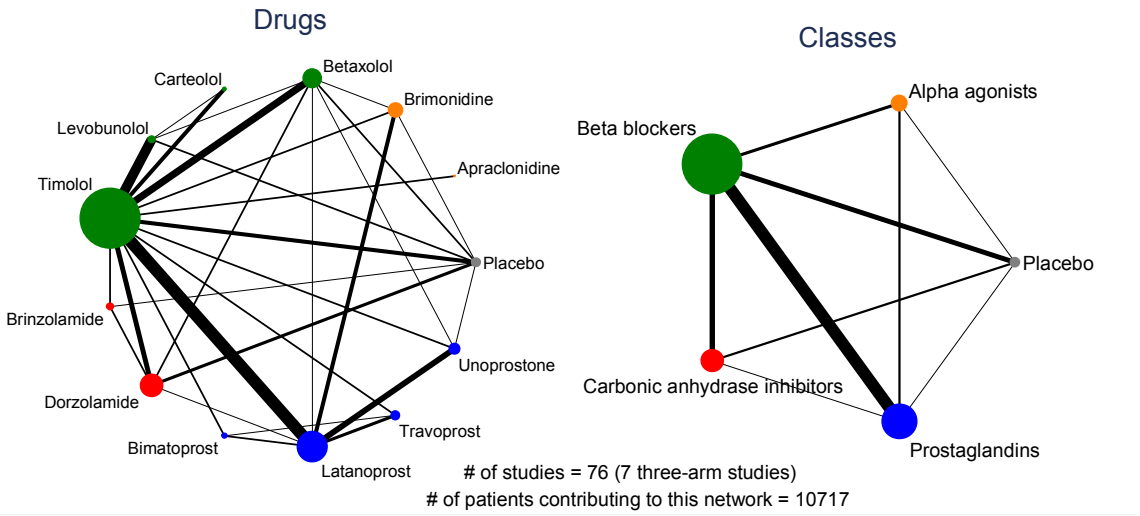
8.3.2 Figure 3b Network graph for studies published up to 1995



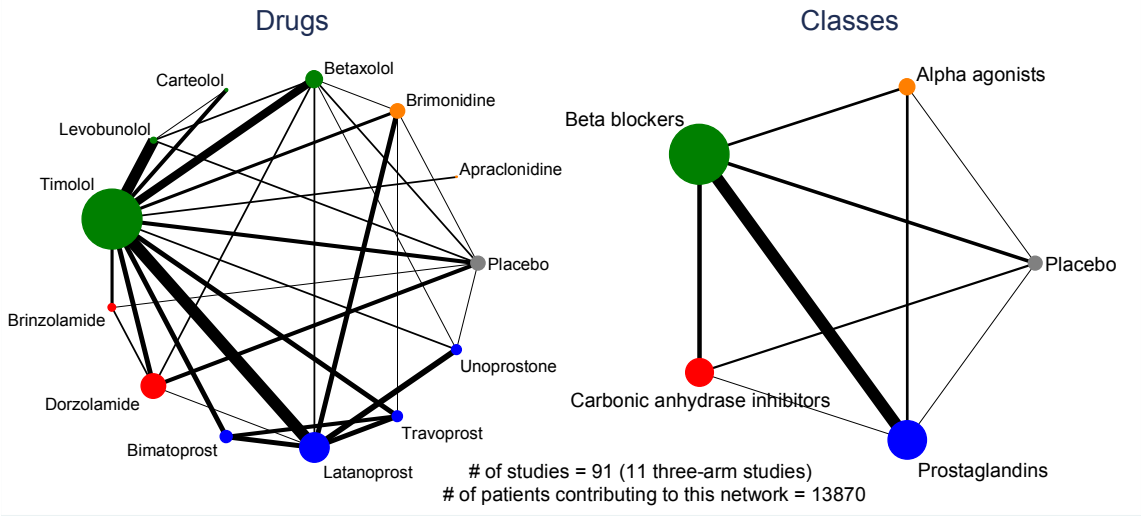
8.3.3 Figure 3c Network graph for studies published up to 2002



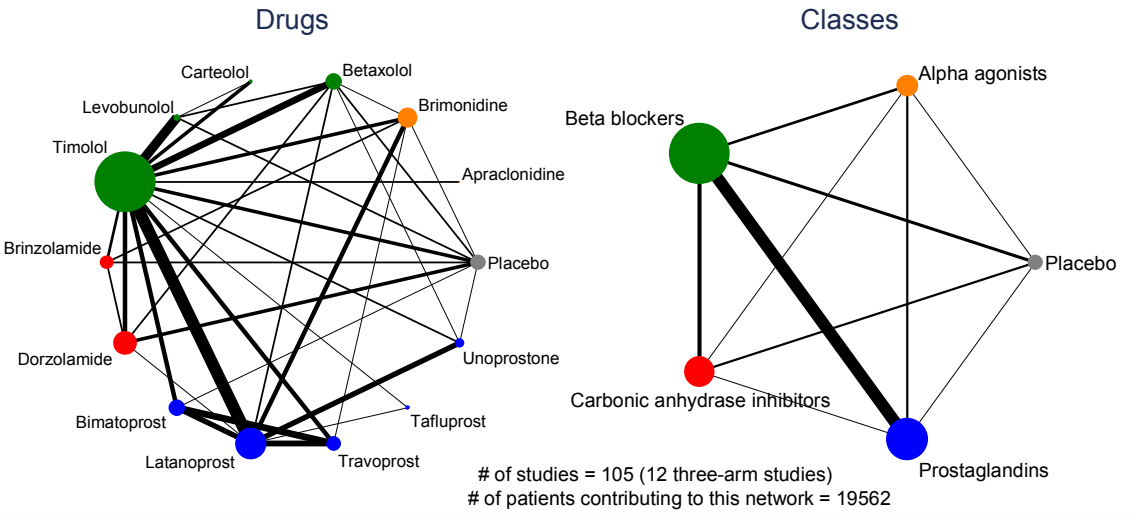
8.3.4 Figure 3d Network graph for studies published up to 2004



8.3.5 Figure 3e Network graph for studies published up to 2009



8.3.6 Figure 3f Network graph for studies published up to 2014



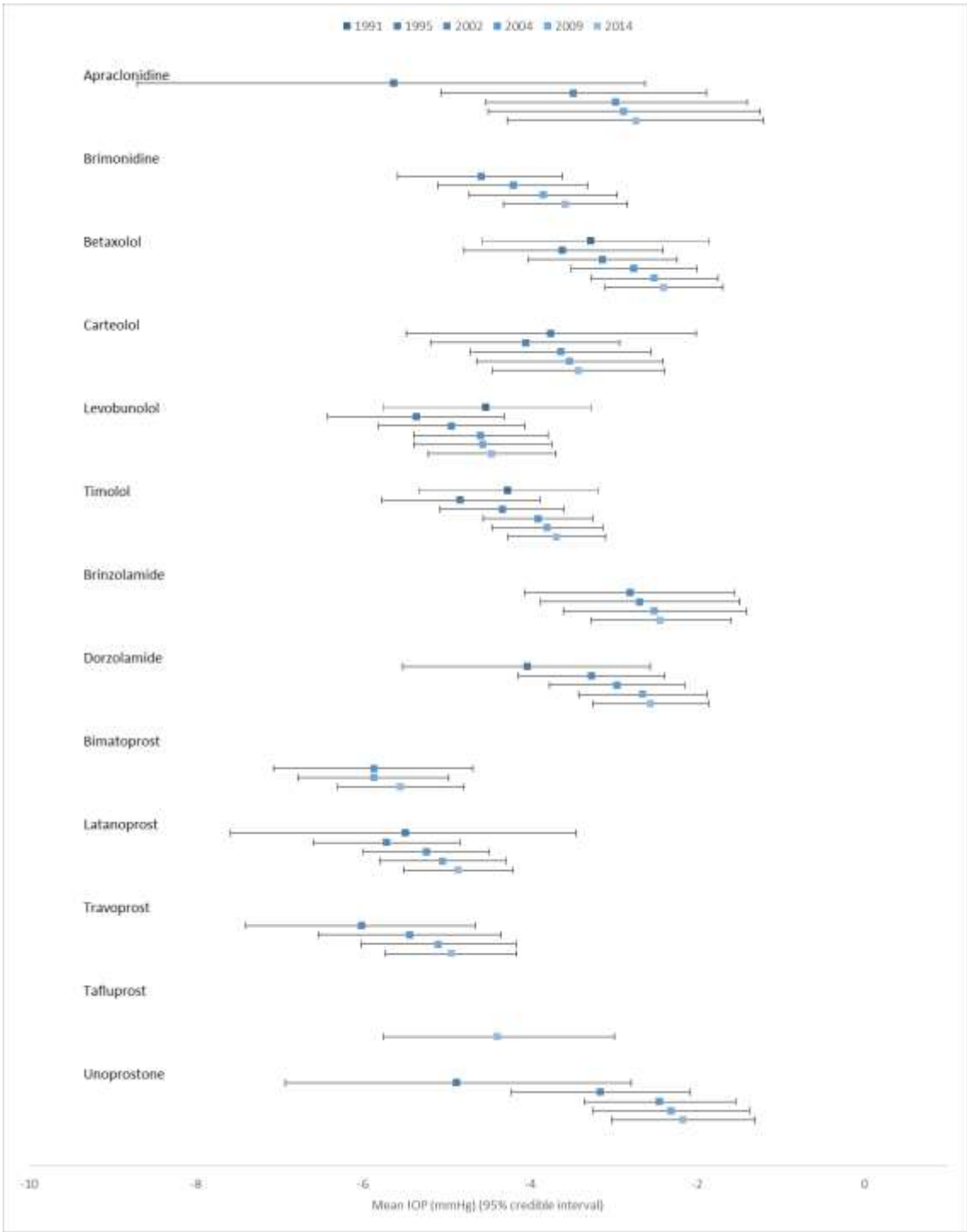
Each node represents one drug. The drugs are color-coded by class. The size of the node is proportional to the number of participants randomized to that drug.

The edges represent direct comparisons (i.e. when there is a line connecting two drugs, the two drugs have been compared directly to each other in a trial). The width of the edge is proportional to the number of trials.

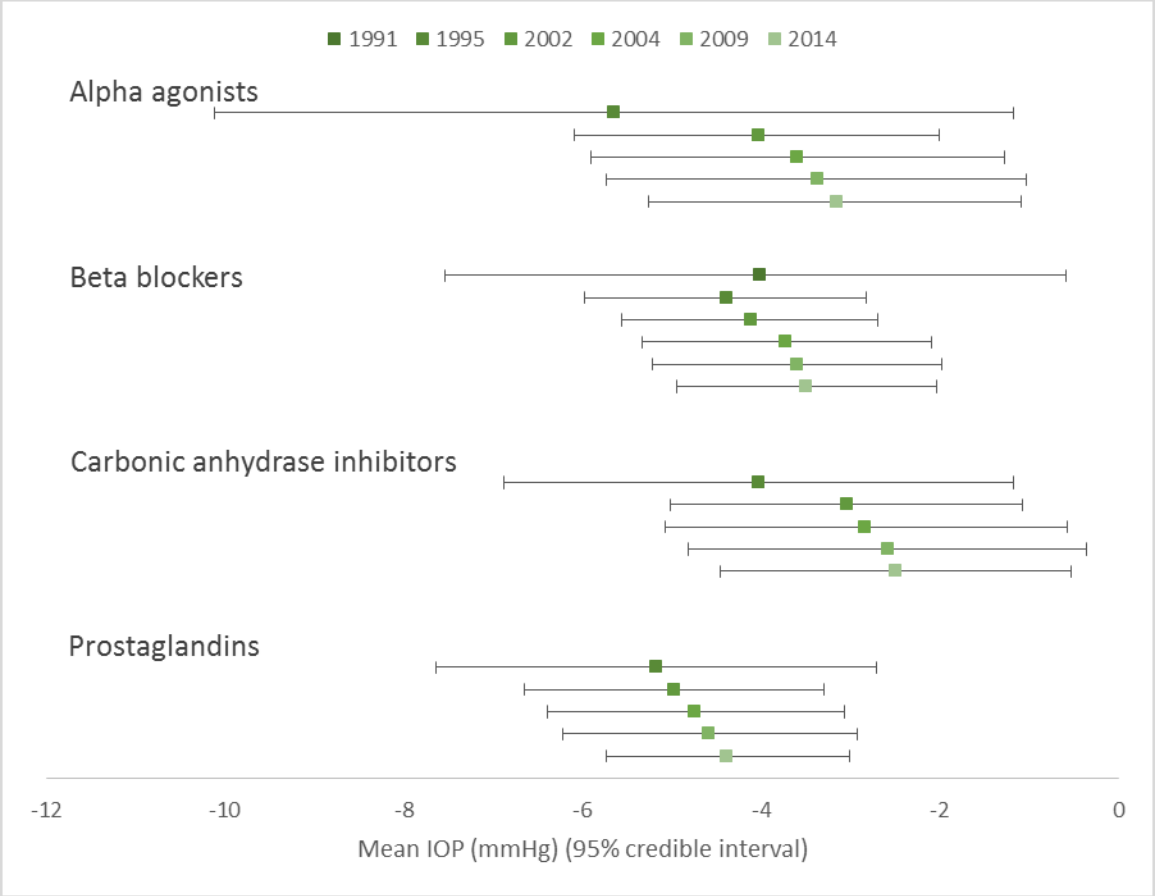
Grey	Placebo/vehicle/no treatment
Orange	Alpha-2 adrenergic agonist
Green	Beta-blocker
Red	Carbonic anhydrase inhibitor
Blue	Prostaglandin analog

8.4 Figure 4 Funnel plots of treatment effect relative to placebo at each network meta-analysis time point

8.4.1 Figure 4a Funnel plot for drug effect relative to placebo



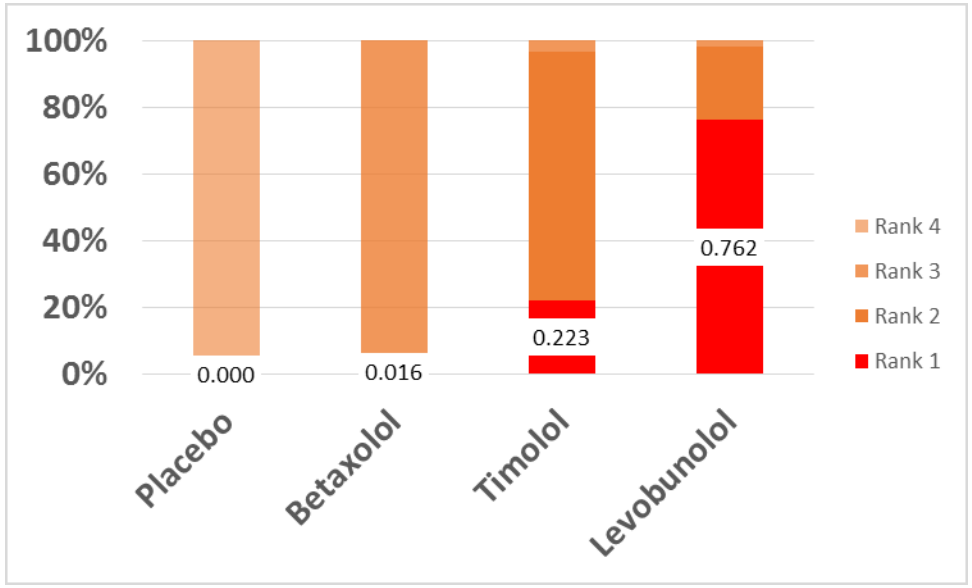
8.4.2 Figure 4b Funnel plot for class effect relative to placebo



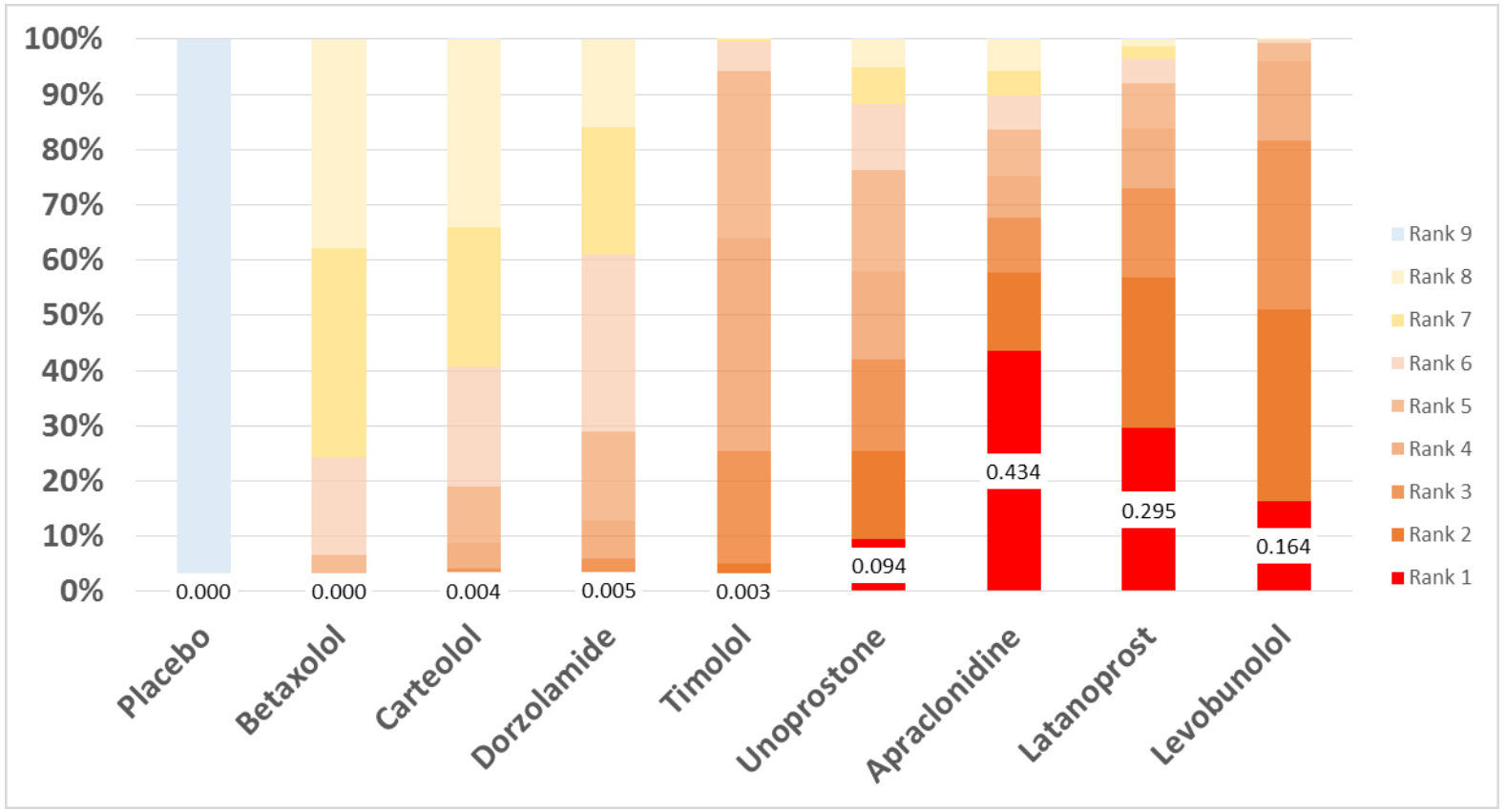
Since glaucoma drugs are expected to lower IOP values, more negative IOP values indicate greater effect.

8.5 Figure 5 Ranking probabilities for any treatment at any position

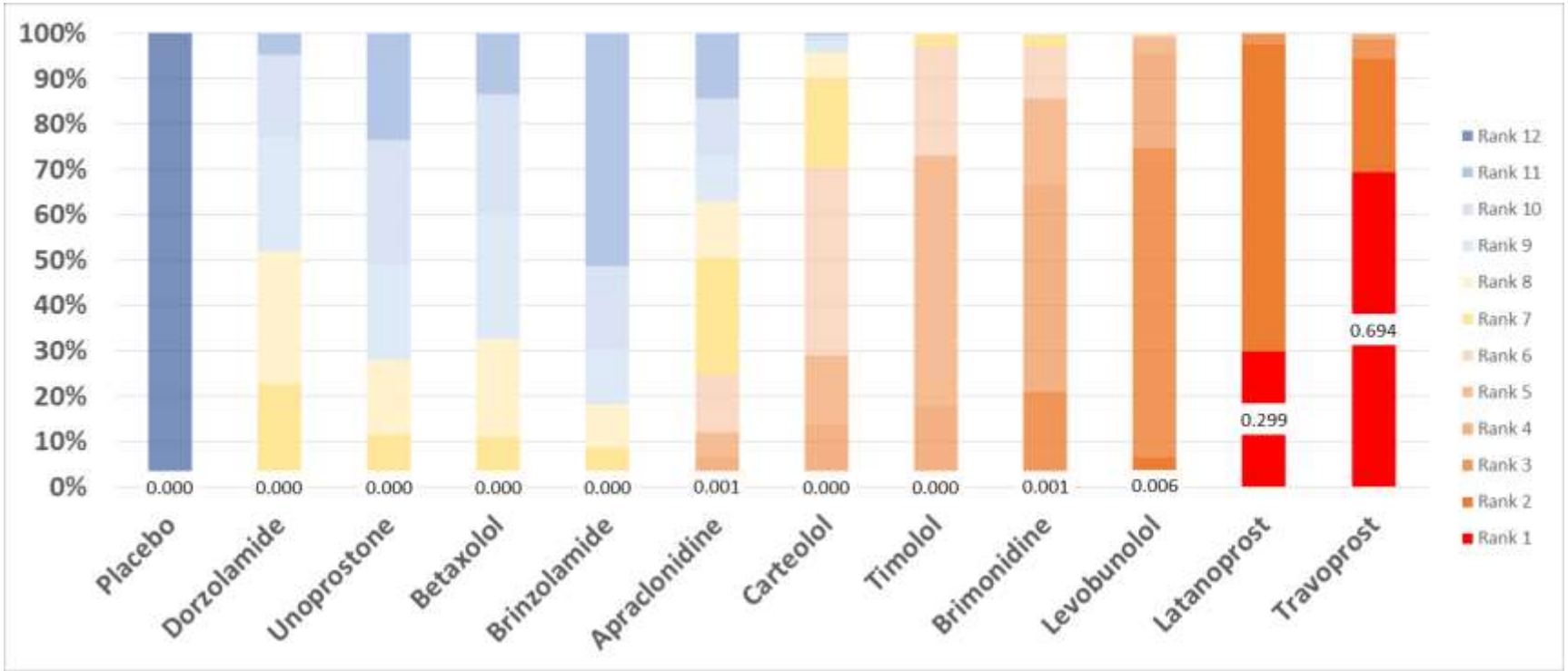
8.5.1 Figure 5a Ranking probabilities for any drug at any position from studies published by 1991



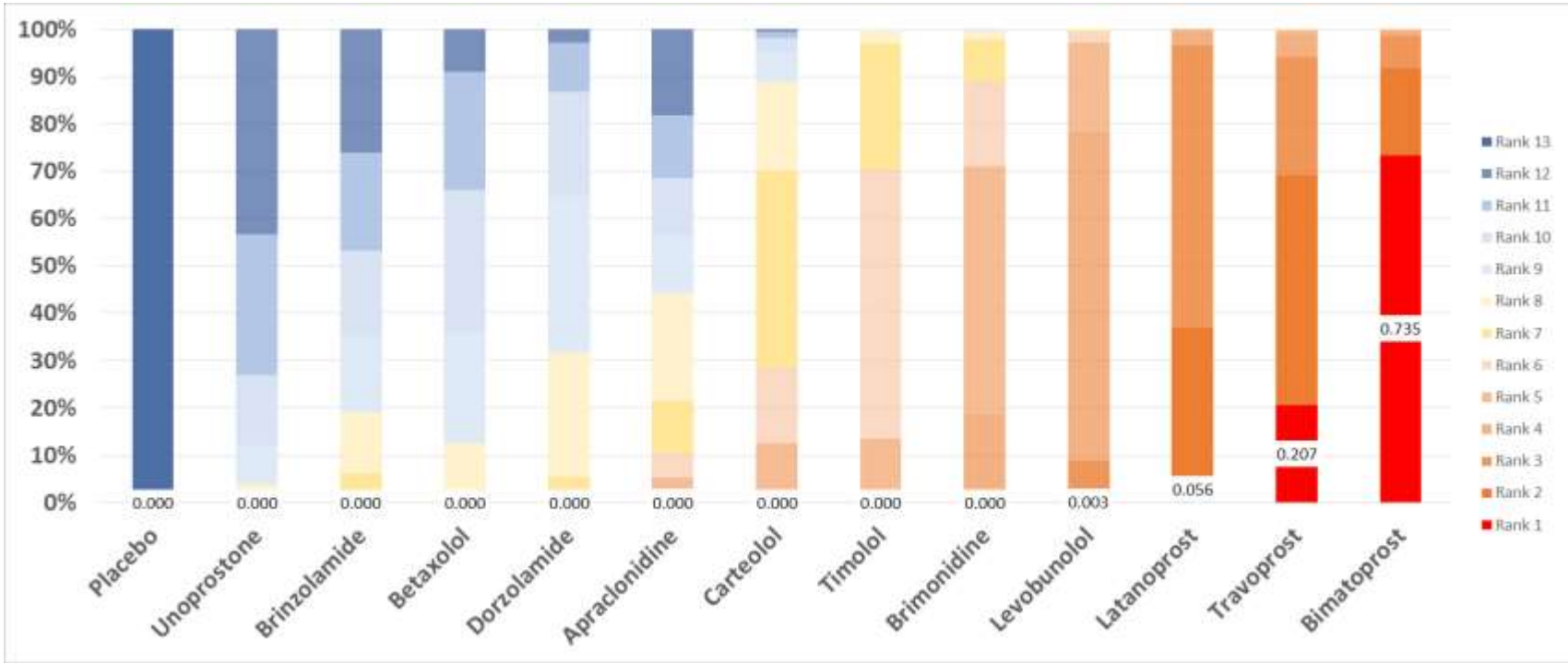
8.5.2 Figure 5b Ranking probabilities for any drug at any position from studies published by 1995



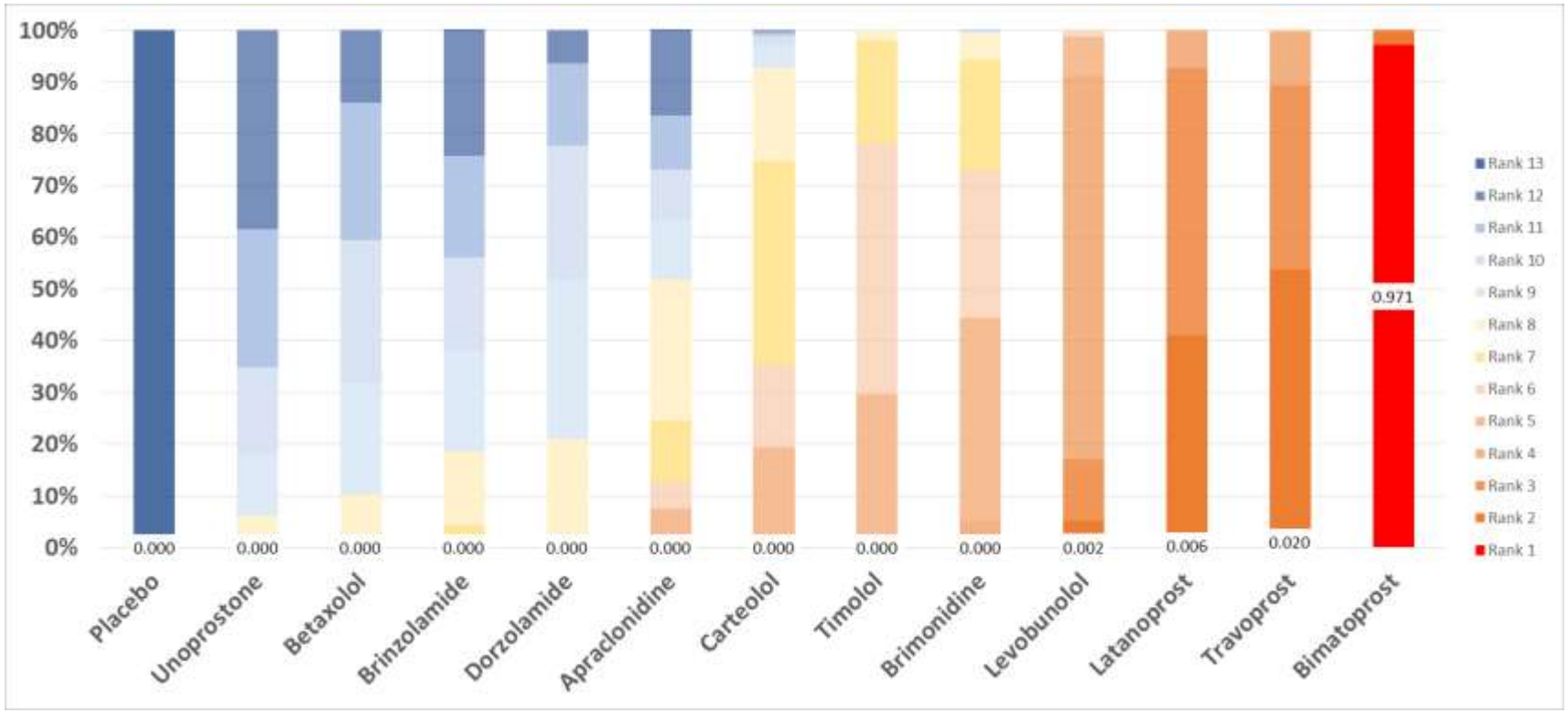
8.5.3 Figure 5c Ranking probabilities for any drug at any position from studies published by 2002



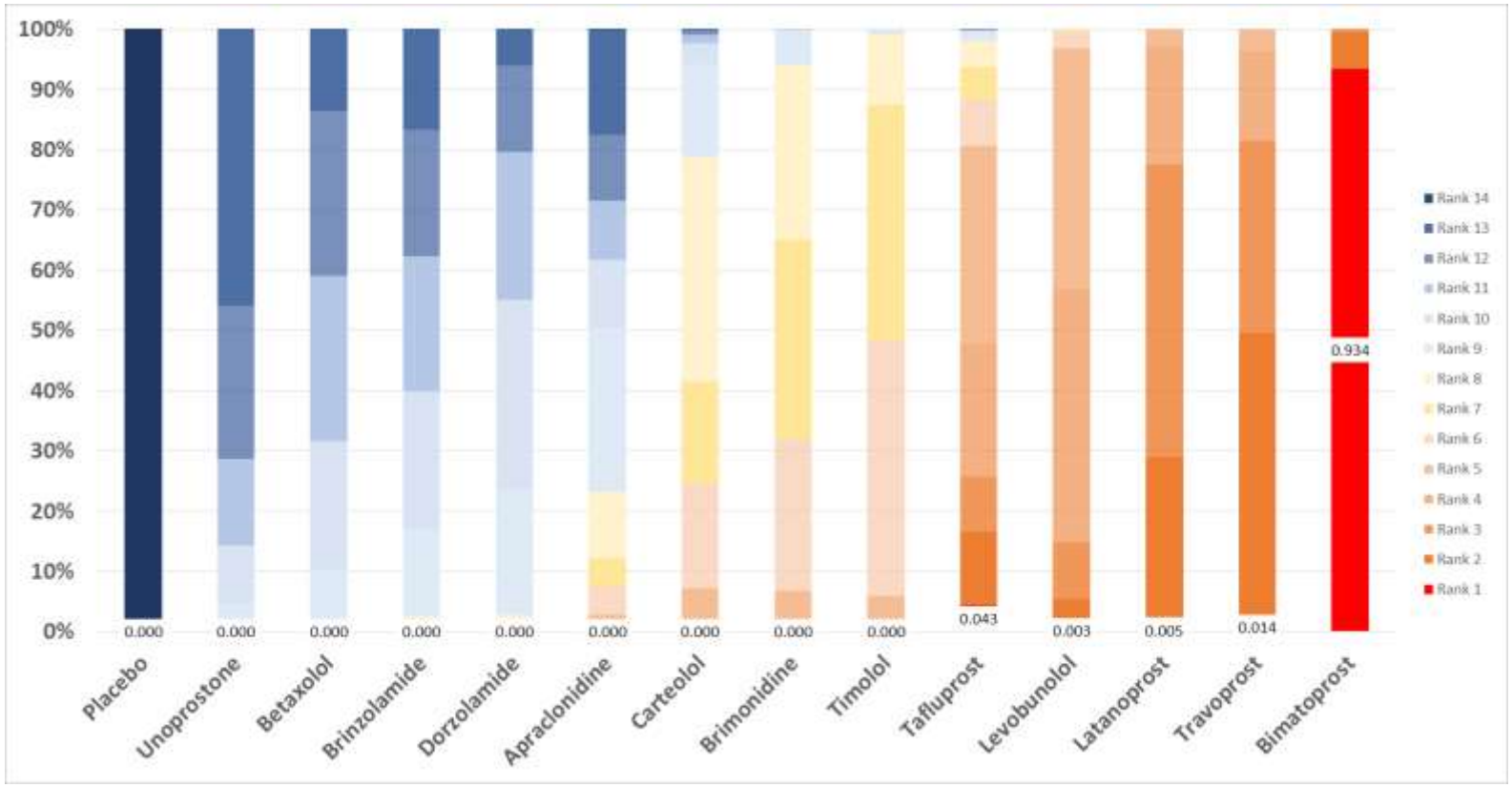
8.5.4 Figure 5d Ranking probabilities for any drug at any position from studies published by 2004



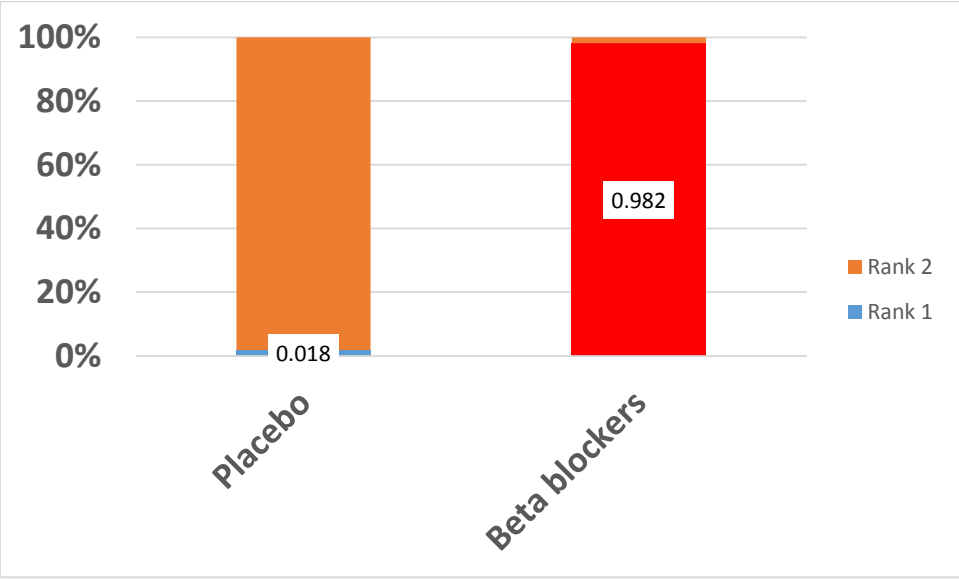
8.5.5 Figure 5e Ranking probabilities for any drug at any position from studies published by 2009



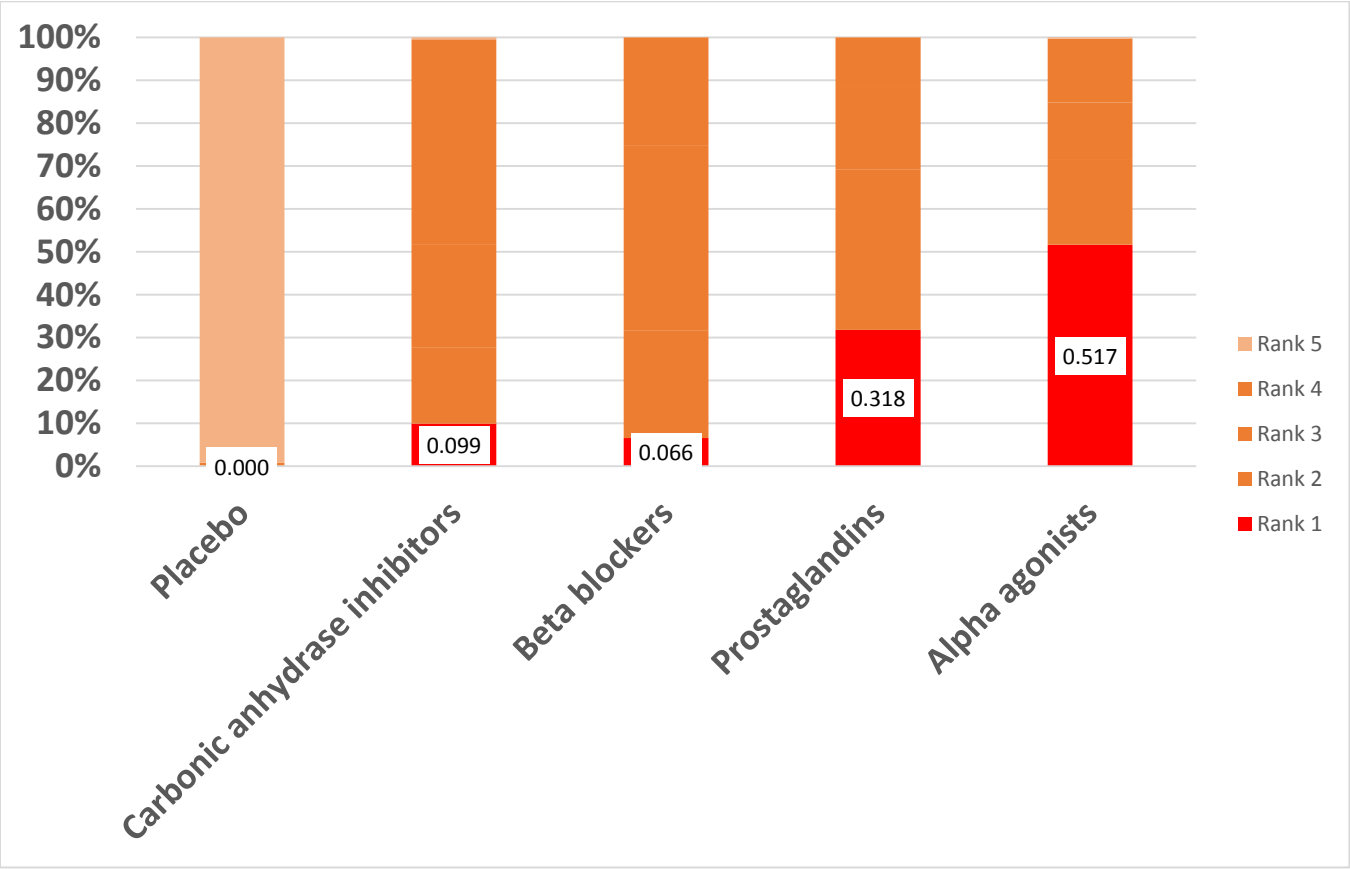
8.5.6 Figure 5f Ranking probabilities for any drug at any position from studies published by 2014



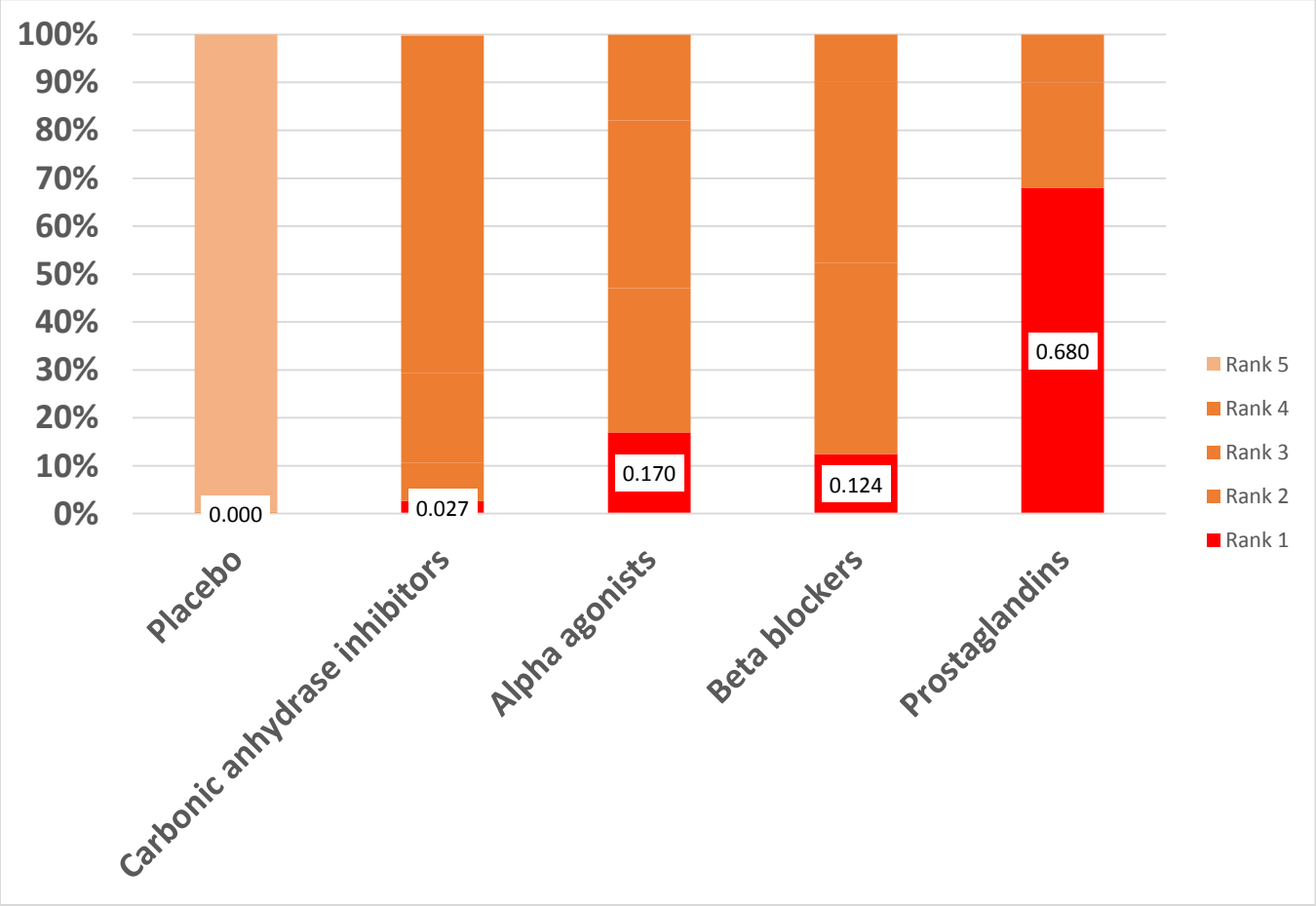
8.5.7 Figure 5g Ranking probabilities for any class at any position from studies published by 1991



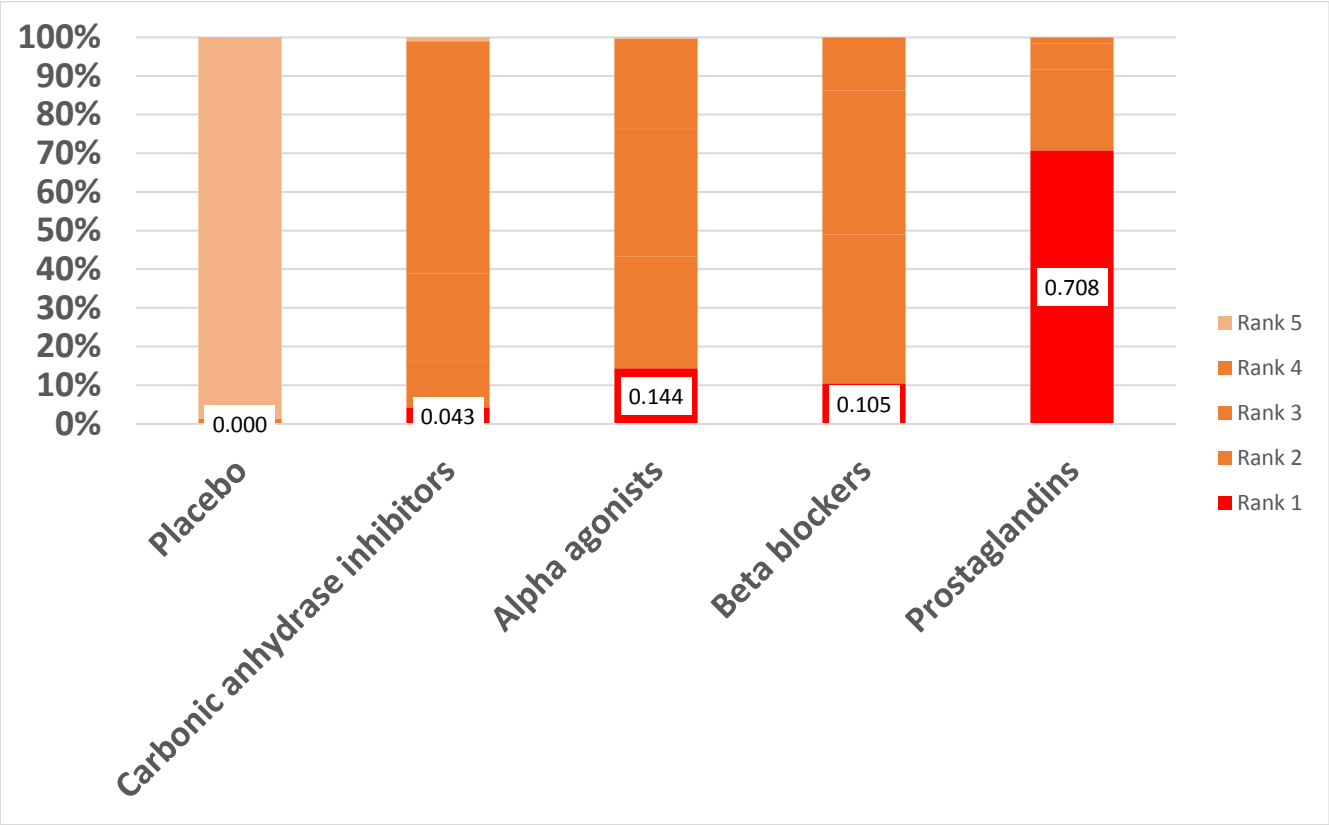
8.5.8 Figure 5h Ranking probabilities for any class at any position from studies published by 1995



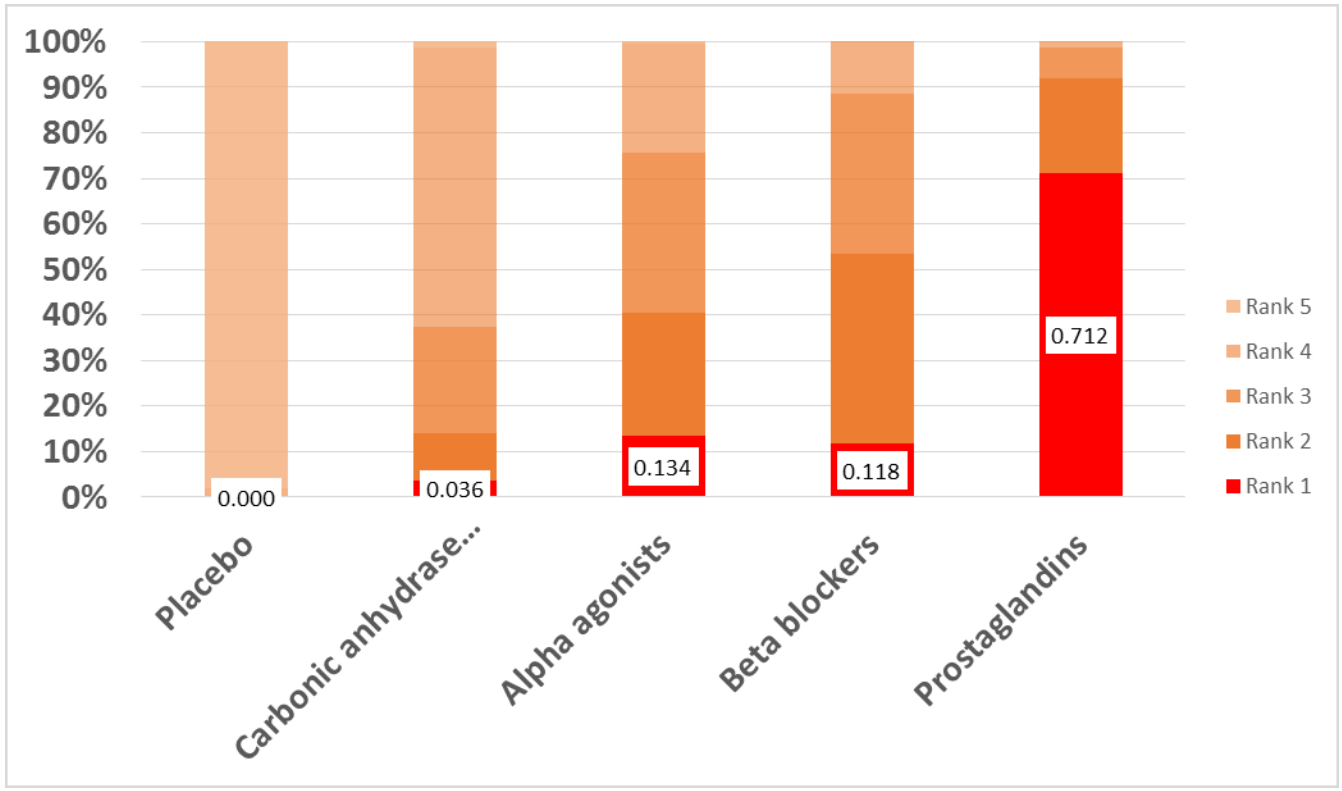
8.5.9 Figure 5i Ranking probabilities for any class at any position from studies published by 2002



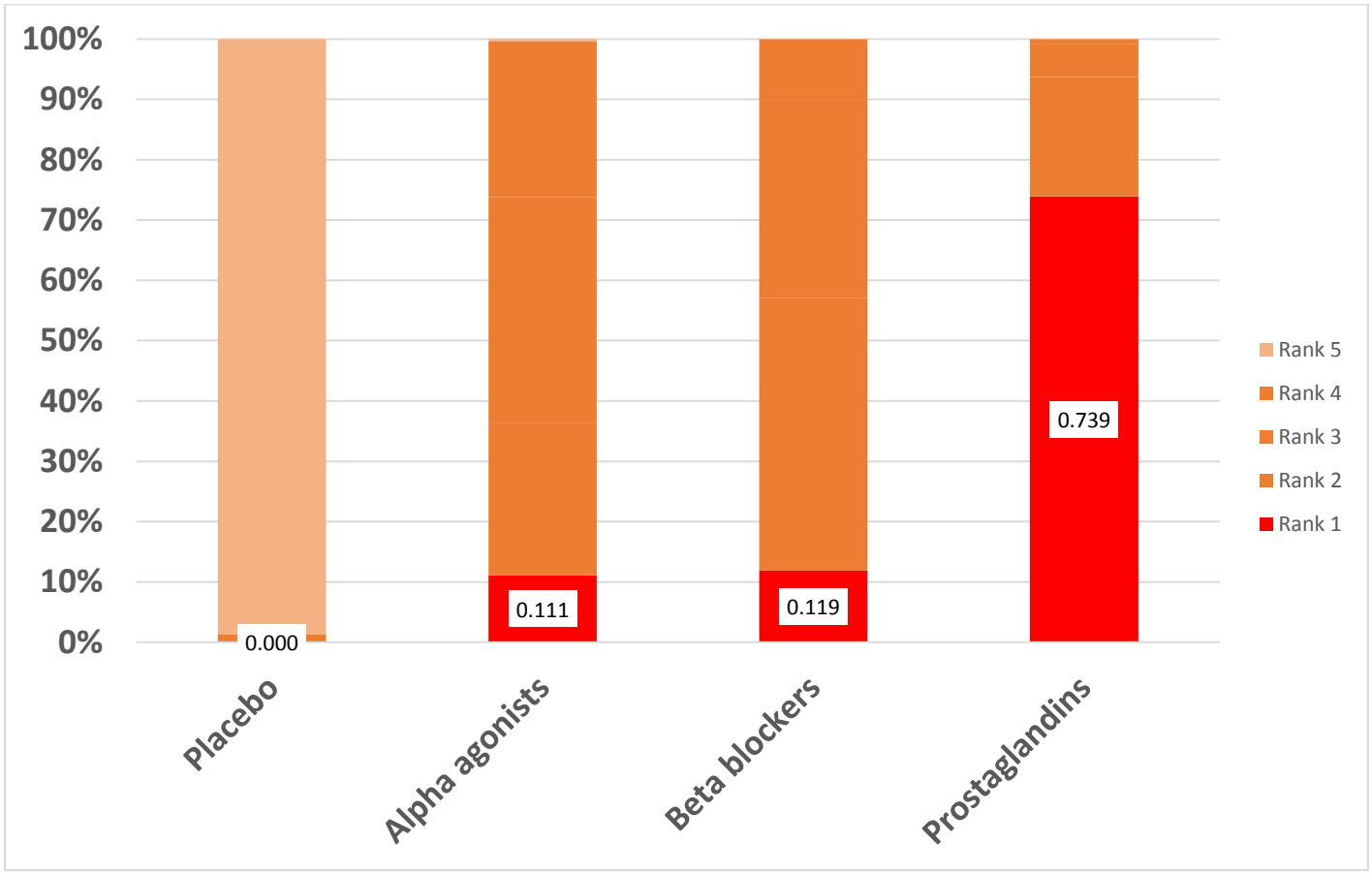
8.5.10 Figure 5j Ranking probabilities for any class at any position from studies published by 2004



8.5.11 Figure 5k Ranking probabilities for any class at any position from studies published by 2009



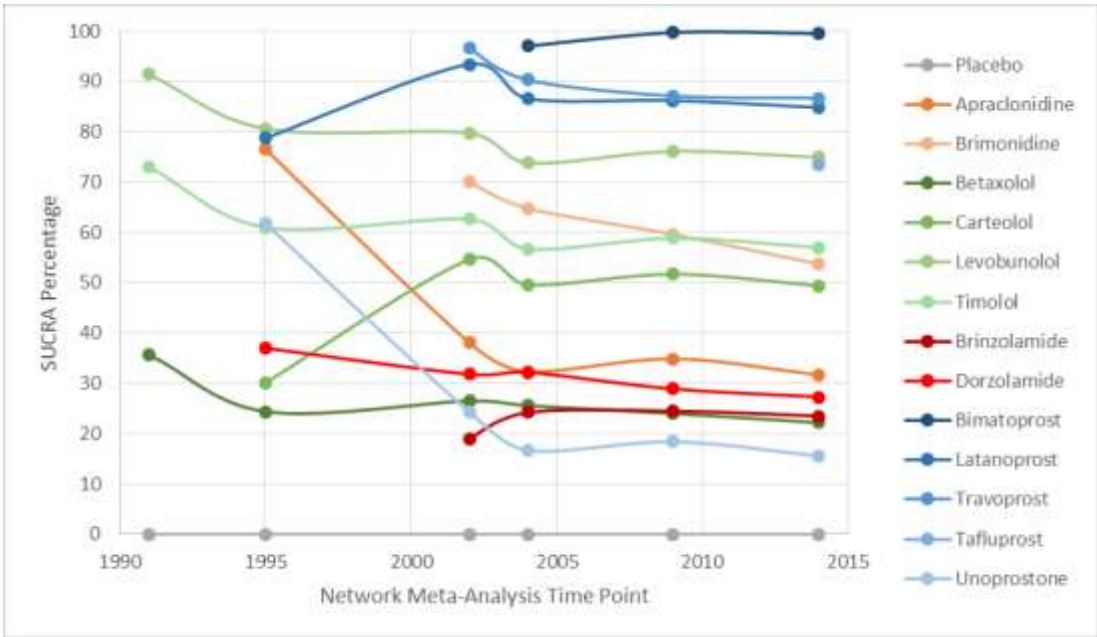
8.5.12 Figure 5l Ranking probabilities for any class at any position from studies published by 2014



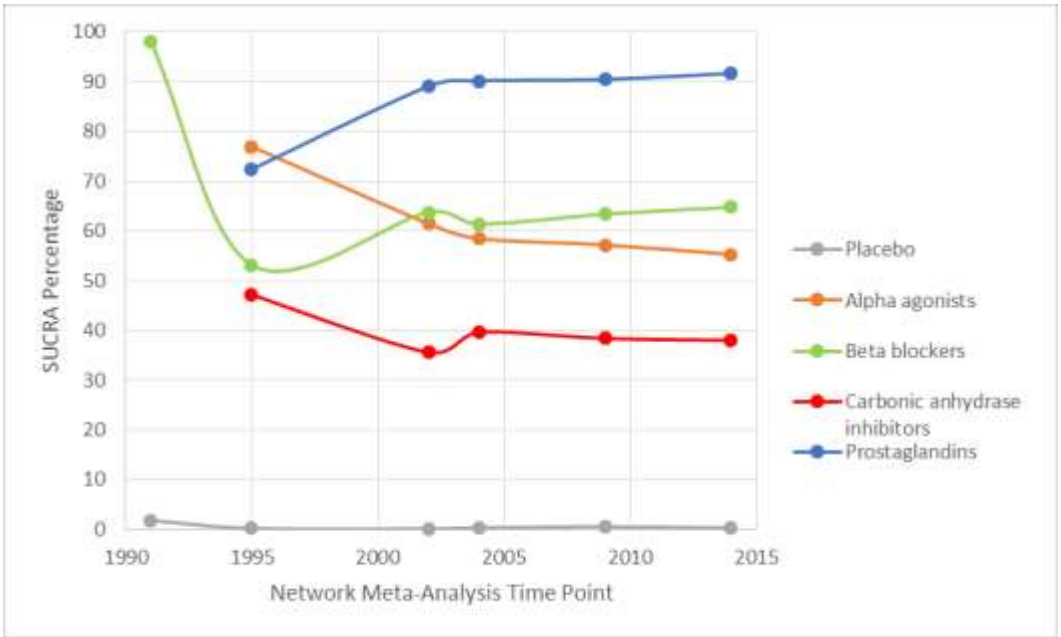
Warmer colors indicate better ranks

8.6 Figure 6 Cumulative ranking of treatments at each network meta-analysis time point

8.6.1 Figure 6a Cumulative ranking of drugs at each network meta-analysis time point



8.6.2 Figure 6b Cumulative ranking of class at each network meta-analysis time point



SUCRA percentage is the probability a treatment has of being among the best treatments (e.g. 100% if certainly the best, 0% if certainly the worst)

Appendix I. Search Strategy

Cochrane Library

#1 MeSH descriptor: [Glaucoma, Open-Angle] explode all trees
#2 MeSH descriptor: [Ocular Hypertension] explode all trees
#3 (open near/2 angle near/2 glaucoma*)
#4 (POAG or OHT)
#5 (((increas* or elevat* or high*) near/3 (ocular or intra-ocular)) and pressure)
#6 {or #1-#5}
#7 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#8 MeSH descriptor: [Timolol] explode all trees
#9 Timolol*
#10 MeSH descriptor: [Metipranolol] explode all trees
#11 Metipranolol*
#12 MeSH descriptor: [Carteolol] explode all trees
#13 Carteolol*
#14 MeSH descriptor: [Levobunolol] explode all trees
#15 Levobunolol*
#16 MeSH descriptor: [Betaxolol] explode all trees
#17 Betaxolol*
#18 MeSH descriptor: [Carbonic Anhydrase Inhibitors] explode all trees
#19 (Carbonic near/2 Anhydrase near/2 Inhibitor*)
#20 MeSH descriptor: [Acetazolamide] explode all trees
#21 Acetazolam*
#22 Brinzolamide*
#23 Dorzolamide*
#24 MeSH descriptor: [Prostaglandins, Synthetic] explode all trees
#25 latanoprost*
#26 travoprost*
#27 bimatoprost*
#28 unoprostone*
#29 tafluprost*
#30 MeSH descriptor: [Antihypertensive Agents] explode all trees
#31 MeSH descriptor: [Pilocarpine] explode all trees
#32 Pilocarpin*
#33 MeSH descriptor: [Epinephrine] explode all trees
#34 epinephrine*
#35 dipivefrin*
#36 MeSH descriptor: [Adrenergic alpha-2 Receptor Agonists] explode all trees

#37 (adrenergic near/2 alpha* near/3 agonist*)
#38 apraclonidin*
#39 brimonidine*
#40 (drug* or medic* or pharmacologic*) near/3 (treat* or therap* or intervent*)
#41 {or #7-#40}
#42 #6 and #41

MEDLINE (OVID)

1. exp clinical trial/ [publication type]
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp glaucoma open angle/
14. exp ocular hypertension/
15. (open adj2 angle adj2 glaucoma$).tw.
16. (POAG or OHT).tw.
17. (((increas$ or elevat$ or high$) adj3 (ocular or intra-ocular)) and pressure).tw.

18. or/13-17
19. exp adrenergic beta antagonists/
20. exp timolol/
21. timolol$.tw.
22. exp metipranolol/
23. metipranolol$.tw.
24. exp carteolol/
25. carteolol$.tw.
26. exp levobunolol/
27. levobunolol$.tw.
28. exp betaxolol/
29. betaxolol$.tw.

30. exp carbonic anhydrase inhibitors/
31. (carbonic adj2 anhydrase adj2 inhibitor$).tw.
32. exp Acetazolamide/
33. acetazolamide$.tw.
34. brinzolamide$.tw.
35. dorzolamide$.tw.
36. exp Prostaglandins, Synthetic/
37. latanoprost$.tw.
38. travoprost$.tw.
39. bimatoprost$.tw.
40. unoprostone$.tw.
41. brimonidine$.tw.
42. exp antihypertensive agents/
43. exp pilocarpine/
44. pilocarpin$.tw.
45. exp epinephrine/
46. epinephrin$.tw.
47. dipivefrin$.tw.
48. exp Adrenergic alpha-2 Receptor Agonists/
49. ((adrenergic adj2 alpha$ adj2 receptor$) or (adrenergic adj2 alpha$ adj2 agonist$)).tw.
50. apraclonidin$.tw.
51. tafluprost$.tw.
52. ((drug$ or medic$ or pharmacologic$) adj3 (treat$ or therap$ or intervent$)).tw.
53. or/19-52
54. 18 and 53
55. 12 and 54

Embase.com

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9

#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'open angle glaucoma'/exp
#34 'intraocular hypertension'/exp
#35 (open NEAR/2 angle):ab,ti AND (angle NEAR/2 glaucoma*):ab,ti
#36 poag:ab,ti OR oht:ab,ti
#37 ((increas* OR elevat* OR high*) NEAR/3 (ocular OR 'intra ocular')):ab,ti AND pressure:ab,ti
#38 #33 OR #34 OR #35 OR #36 OR #37
#39 'beta adrenergic receptor blocking agent'/exp
#40 'timolol'/exp
#41 timolol*:ab,ti
#42 'metipranolol'/exp
#43 metipranolol*:ab,ti
#44 'carteolol'/exp
#45 carteolol*:ab,ti
#46 'levobunolol'/exp
#47 levobunolol*:ab,ti

#48 'betaxolol'/exp
#49 betaxolol*:ab,ti
#50 'carbonate dehydratase inhibitor'/exp
#51 (carbonic NEAR/2 anhydrase):ab,ti AND (anhydrase NEAR/2 inhibitor*):ab,ti
#52 'acetazolamide'/exp
#53 acetazolamide*:ab,ti
#54 brinzolamide*:ab,ti
#55 dorzolamide*:ab,ti
#56 'latanoprost'/exp
#57 latanoprost*:ab,ti
#58 'travoprost'/exp
#59 travoprost*:ab,ti
#60 'bimatoprost'/exp
#61 bimatoprost*:ab,ti
#62 'unoprostone isopropyl ester'/exp
#63 unoprostone*:ab,ti
#64 'brimonidine'/exp
#65 brimonidine*:ab,ti
#66 'antihypertensive agent'/exp
#67 'pilocarpine'/exp
#68 pilocarpin*:ab,ti
#69 'adrenalin'/exp
#70 epinephrin*:ab,ti
#71 dipivefrin*:ab,ti
#72 'alpha 2 adrenergic receptor stimulating agent'/exp
#73 (adrenergic NEAR/2 alpha*):ab,ti AND (alpha* NEAR/2 agonist*):ab,ti
#74 apraclonidin*:ab,ti
#75 'tafluprost'/exp
#76 tafluprost*:ab,ti
#77 ((drug* OR medic* OR pharmacologic*) NEAR/3 (treat* OR therap* OR intervent*)):ab,ti
#78 #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77
#79 #38 AND #78
#80 #32 AND #79

PubMed

#1 ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])

#2 (open[tw] AND angle[tw] AND glaucoma*[tw]) NOT Medline[sb]

#3 (POAG[tw] OR OHT[tw]) NOT Medline[sb]

#4 (((increase*[tw] OR elevat*[tw] OR high*[tw]) AND (ocular[tw] OR intra-ocular[tw])) AND pressure[tw]) NOT Medline[sb]

#5 #2 OR #3 OR #4

#6 timolol*[tw] NOT Medline[sb]

#7 metipranolol*[tw] NOT Medline[sb]

#8 carteolol*[tw] NOT Medline[sb]

#9 levobunolol*[tw] NOT Medline[sb]

#10 betaxolol*[tw] NOT Medline[sb]

#11 (carbonic[tw] AND anhydrase[tw] AND inhibitor*[tw]) NOT Medline[sb]

#12 acetazolamide*[tw] NOT Medline[sb]

#13 brinzolamide*[tw] NOT Medline[sb]

#14 dorzolamide*[tw] NOT Medline[sb]

#15 latanoprost*[tw] NOT Medline[sb]

#16 travoprost*[tw] NOT Medline[sb]

#17 bimatoprost*[tw] NOT Medline[sb]

#18 unoprostone*[tw] NOT Medline[sb]

#19 brimonidine*[tw] NOT Medline[sb]

#20 pilocarpin*[tw] NOT Medline[sb]

#21 epinephrin*[tw] NOT Medline[sb]

#22 dipivefrin* NOT Medline[sb]

#23 ((adrenergic[tw] AND alpha*[tw] AND receptor*[tw]) OR (adrenergic[tw] AND alpha*[tw] AND agonist*[tw])) NOT Medline[sb]

#24 apraclonidin*[tw] NOT Medline[sb]

#25 tafluprost*[tw] NOT Medline[sb]

#26 ((drug*[tw] OR medic*[tw] OR pharmacologic*[tw]) AND (treat*[tw] OR therap*[tw] OR intervent*[tw])) NOT Medline[sb]

#27 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26

#28 #5 AND #27

#29 #1 AND #2

Appendix II. References to included studies

1. Radius RL. Use of betaxolol in the reduction of elevated intraocular pressure. *Arch Ophthalmol* 1983; 101(6): 898-900.
2. Berry DP, Jr., Van Buskirk EM, Shields MB. Betaxolol and timolol. A comparison of efficacy and side effects. *Arch Ophthalmol* 1984; 102(1): 42-5.
3. Bensinger RE, Keates EU, Gofman JD, Novack GD, Duzman E. Levobunolol. A three-month efficacy study in the treatment of glaucoma and ocular hypertension. *Arch Ophthalmol* 1985; 103(3): 375-8.
4. Berson FG, Cohen HB, Foerster RJ, Lass JH, Novack GD, Duzman E. Levobunolol compared with timolol for the long-term control of elevated intraocular pressure. *Arch Ophthalmol* 1985; 103(3): 379-82.
5. Cinotti A, Cinotti D, Grant W, et al. Levobunolol vs timolol for open-angle glaucoma and ocular hypertension. *Am J Ophthalmol* 1985; 99(1): 11-7.
6. Ober M, Scharrer A, David R, et al. Long-term ocular hypotensive effect of levobunolol: results of a one-year study. *Br J Ophthalmol* 1985; 69(8): 593-9.
7. Stryz JR, Merte HJ. [Pressure lowering effect and side effects of 0.5% and 1.0% levobunolol eyedrops, compared with 0.5% timolol eyedrops in patients with open-angle glaucoma]. *Klin Monbl Augenheilkd* 1985; 187(6): 537-44.
8. Stewart RH, Kimbrough RL, Ward RL. Betaxolol vs timolol. A six-month double-blind comparison. *Arch Ophthalmol* 1986; 104(1): 46-8.
9. Boozman FW, 3rd, Carriker R, Foerster R, Allen RC, Novack GD, Batoosingh AL. Long-term evaluation of 0.25% levobunolol and timolol for therapy for elevated intraocular pressure. *Arch Ophthalmol* 1988; 106(5): 614-8.
10. Feghali JG, Kaufman PL, Radius RL, Mandell AI. A comparison of betaxolol and timolol in open angle glaucoma and ocular hypertension. *Acta Ophthalmol (Copenh)* 1988; 66(2): 180-6.
11. Freyler H, Novack GD, Menapace R, Skorpik C, Mordaunt J, Batoosingh AL. [Comparison of the effectiveness and safety of levobunolol and timolol in ocular hypertension and chronic open-angle glaucoma]. *Klin Monbl Augenheilkd* 1988; 193(3): 257-60.
12. Long DA, Johns GE, Mullen RS, et al. Levobunolol and betaxolol. A double-masked controlled comparison of efficacy and safety in patients with elevated intraocular pressure. *Ophthalmology* 1988; 95(6): 735-41.

13. Seamone C, LeBlanc R, Saheb N, Novack G. Efficacy of twice-daily levobunolol in the treatment of elevated intraocular pressure. *Can J Ophthalmol* 1988; 23(4): 168-70.

14. Epstein DL, Krug JH, Jr., Hertzmark E, Remis LL, Edelstein DJ. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. *Ophthalmology* 1989; 96(10): 1460-7.

15. Kass MA, Gordon MO, Hoff MR, et al. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals. A randomized, double-masked, long-term clinical trial. *Arch Ophthalmol* 1989; 107(11): 1590-8.

16. Yoshiaki K, Ikuo A, Makoto A. Clinical evaluation of betaxolol hydrochloride in the treatment of primary open angle glaucoma and ocular hypertension. Multi-center double-masked study in comparison with timolol. *Rinsho Hyoka (Clinical Evaluation)* 1989; 17(2): 243-74.

17. Schulzer M, Drance SM, Douglas GR. A comparison of treated and untreated glaucoma suspects. *Ophthalmology* 1991; 98(3): 301-7.

18. Silverstone D, Zimmerman T, Choplin N, et al. Evaluation of once-daily levobunolol 0.25% and timolol 0.25% therapy for increased intraocular pressure. *Am J Ophthalmol* 1991; 112(1): 56-60.

19. Beehler CC, Stewart WC, Macdonald DK, et al. A comparison of the ocular hypotensive efficacy of twice-daily 0.25% levobunolol to 0.5% timolol in patients previously treated with 0.5% timolol. *J Glaucoma* 1992; 1(4): 237-42.

20. Flammer J, Kitazawa Y, Bonomi L, et al. Influence of carteolol and timolol on IOP an visual fields in glaucoma: a multi-center, double-masked, prospective study. *Eur J Ophthalmol* 1992; 2(4): 169-74.

21. Azuma I, Masuda K, Kitazawa Y, Takase M, Yamamura H. Double-masked comparative study of UF-021 and timolol ophthalmic solutions in patients with primary open-angle glaucoma or ocular hypertension. *Jpn J Ophthalmol* 1993; 37(4): 514-25.

22. Nagasubramanian S, Hitchings RA, Demailly P, et al. Comparison of apraclonidine and timolol in chronic open-angle glaucoma. A three-month study. *Ophthalmology* 1993; 100(9): 1318-23.

23. Wilkerson M, Cyrlin M, Lippa EA, et al. Four-week safety and efficacy study of dorzolamide, a novel, active topical carbonic anhydrase inhibitor. *Arch Ophthalmol* 1993; 111(10): 1343-50.

24. Behrens-Baumann W, Kimmich F, Walt JG, Lue J. A comparison of the ocular hypotensive efficacy and systemic safety of 0.5% levobunolol and 2% carteolol. *Ophthalmologica* 1994; 208(1): 32-6.

25. Kitazawa Y. Phase III comparative study of MK-507 ophthalmic solution in primary open-angle glaucoma and ocular hypertension. *Folia Ophthalmol Jpn* 1994; 45(9): 1023-33.

26. Ravalico G, Salvetat L, Toffoli G, Pastori G, Croce M, Battaglia P. Ocular hypertension: A follow-up study in treated and untreated patients. *NEW TRENDS OPHTHALMOL* 1994; 9(2): 97-101.

27. Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Scandinavian Latanoprost Study Group. *Ophthalmology* 1995; 102(12): 1743-52.

28. Schwartz B, Lavin P, Takamoto T, Araujo DF, Smits G. Decrease of optic disc cupping and pallor of ocular hypertensives with timolol therapy. *Acta Ophthalmol Scand Suppl* 1995; (215): 5-21.

29. Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. International Dorzolamide Study Group. *Arch Ophthalmol* 1995; 113(8): 1009-16.

30. Fristrom B. A 6-month, randomized, double-masked comparison of latanoprost with timolol in patients with open angle glaucoma or ocular hypertension. *Acta Ophthalmol Scand* 1996; 74(2): 140-4.

31. Mishima HK, Masuda K, Kitazawa Y, Azuma I, Araie M. A comparison of latanoprost and timolol in primary open-angle glaucoma and ocular hypertension. A 12-week study. *Arch Ophthalmol* 1996; 114(8): 929-32.

32. Schuman JS. Clinical experience with brimonidine 0.2% and timolol 0.5% in glaucoma and ocular hypertension. *Surv Ophthalmol* 1996; 41 Suppl 1: S27-37.

33. Serle JB. A comparison of the safety and efficacy of twice daily brimonidine 0.2% versus betaxolol 0.25% in subjects with elevated intraocular pressure. The Brimonidine Study Group III. *Surv Ophthalmol* 1996; 41 Suppl 1: S39-47.

34. Stewart WC, Laibovitz R, Horwitz B, Stewart RH, Ritch R, Kottler M. A 90-day study of the efficacy and side effects of 0.25% and 0.5% apraclonidine vs 0.5% timolol. Apraclonidine Primary Therapy Study Group. *Arch Ophthalmol* 1996; 114(8): 938-42.

35. Watson P, Stjernschantz J. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. The Latanoprost Study Group. *Ophthalmology* 1996; 103(1): 126-37.

36. Yamamoto T, Kitazawa Y, Noma A, et al. The effects of the beta-adrenergic-blocking agents, timolol and carteolol, on plasma lipids and lipoproteins in Japanese glaucoma patients. *J Glaucoma* 1996; 5(4): 252-7.

37. Kitazawa Y, Azuma I, Shirato S, et al. Phase III Clinical Study of AG-901 Ophthalmic Solution on Primary Open-Angle Glaucoma and Ocular Hypertension: A Multicenter, Double-Blind Comparison with 0.5% Timolol Maleate. *Journal of Clinical Therapeutics and Medicines* 1997; 13(11): 2975-91.

38. Stewart WC, Cohen JS, Netland PA, Weiss H, Nussbaum LL. Efficacy of carteolol hydrochloride 1% vs timolol maleate 0.5% in patients with increased intraocular pressure. Nocturnal Investigation of Glaucoma Hemodynamics Trial Study Group. *Am J Ophthalmol* 1997; 124(4): 498-505.

39. Boyle JE, Ghosh K, Gieser DK, Adamsons IA. A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol and dorzolamide. Dorzolamide-Timolol Study Group. *Ophthalmology* 1998; 105(10): 1945-51.

40. Clineschmidt CM, Williams RD, Snyder E, Adamsons IA. A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. Dorzolamide-Timolol Combination Study Group. *Ophthalmology* 1998; 105(10): 1952-9.

41. Diestelhorst M, Almegard B. Comparison of two fixed combinations of latanoprost and timolol in open-angle glaucoma. *Graefes Arch Clin Exp Ophthalmol* 1998; 236(8): 577-81.

42. LeBlanc RP. Twelve-month results of an ongoing randomized trial comparing brimonidine tartrate 0.2% and timolol 0.5% given twice daily in patients with glaucoma or ocular hypertension. Brimonidine Study Group 2. *Ophthalmology* 1998; 105(10): 1960-7.

43. Rusk C, Sharpe E, Laurence J, Polis A, Adamsons I. Comparison of the efficacy and safety of 2% dorzolamide and 0.5% betaxolol in the treatment of elevated intraocular pressure. Dorzolamide Comparison Study Group. *Clin Ther* 1998; 20(3): 454-66.

44. Silver LH. Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. Brinzolamide Primary Therapy Study Group. *Am J Ophthalmol* 1998; 126(3): 400-8.

45. Bojic L, Bagatin J, Ivanisevic M, Hozo I, Racic G, Karelovic D. Influence of betaxolol and timolol on the venous tone in glaucoma patients. *Int Ophthalmol* 1999; 23(3): 149-53.

46. Stewart WC, Dubiner HB, Mundorf TK, et al. Effects of carteolol and timolol on plasma lipid profiles in older women with ocular hypertension or primary open-angle glaucoma. *Am J Ophthalmol* 1999; 127(2): 142-7.

47. Toris CB, Camras CB, Yablonski ME. Acute versus chronic effects of brimonidine on aqueous humor dynamics in ocular hypertensive patients. *Am J Ophthalmol* 1999; 128(1): 8-14.

48. Alm A, Widengard I. Latanoprost: experience of 2-year treatment in Scandinavia. *Acta Ophthalmol Scand* 2000; 78(1): 71-6.

49. O'Donoghue EP. A comparison of latanoprost and dorzolamide in patients with glaucoma and ocular hypertension: a 3 month, randomised study. Ireland Latanoprost Study Group. *Br J Ophthalmol* 2000; 84(6): 579-82.

50. Sall K. The efficacy and safety of brinzolamide 1% ophthalmic suspension (Azopt) as a primary therapy in patients with open-angle glaucoma or ocular hypertension. Brinzolamide Primary Therapy Study Group. *Surv Ophthalmol* 2000; 44 Suppl 2: S155-62.

51. Bron AM, Denis P, Nordmann JP, Rouland JF, Sellem E, Johansson M. Additive IOP-reducing effect of latanoprost in patients insufficiently controlled on timolol. *Acta ophthalmologica Scandinavica* 2001; 79(3): 289-93.

52. DuBiner HB, Mroz M, Shapiro AM, Dirks MS, Brimonidine vs. Latanoprost Study G. A comparison of the efficacy and tolerability of brimonidine and latanoprost in adults with open-angle glaucoma or ocular hypertension: a three-month, multicenter, randomized, double-masked, parallel-group trial. *Clin Ther* 2001; 23(12): 1969-83.

53. Kobayashi H, Kobayashi K, Okinami S. A comparison of intraocular pressure-lowering effect of prostaglandin F2 -alpha analogues, latanoprost, and unoprostone isopropyl. *J Glaucoma* 2001; 10(6): 487-92.

54. Susanna R, Jr., Giampani J, Jr., Borges AS, Vessani RM, Jordao ML. A double-masked, randomized clinical trial comparing latanoprost with unoprostone in patients with open-angle glaucoma or ocular hypertension. *Ophthalmology* 2001; 108(2): 259-63.

55. Aung T, Chew PT, Oen FT, et al. Additive effect of unoprostone and latanoprost in patients with elevated intraocular pressure. *Br J Ophthalmol* 2002; 86(1): 75-9.

56. Bergstrand IC, Heijl A, Harris A. Dorzolamide and ocular blood flow in previously untreated glaucoma patients: a controlled double-masked study. *Acta Ophthalmol Scand* 2002; 80(2): 176-82.

57. Halpern MT, Covert DW, Robin AL. Projected impact of travoprost versus both timolol and latanoprost on visual field deficit progression and costs among black glaucoma subjects. *Trans Am Ophthalmol Soc*. 2002;100:109-17

58. Fellman RL, Sullivan EK, Ratliff M, et al. Comparison of travoprost 0.0015% and 0.004% with timolol 0.5% in patients with elevated

intraocular pressure: a 6-month, masked, multicenter trial. *Ophthalmology* 2002; 109(5): 998-1008.

59. Higginbotham EJ, Feldman R, Stiles M, Dubiner H, Fixed Combination Investigative G. Latanoprost and timolol combination therapy vs monotherapy: one-year randomized trial. *Arch Ophthalmol* 2002; 120(7): 915-22.

60. Jampel HD, Bacharach J, Sheu WP, et al. Randomized clinical trial of latanoprost and unoprostone in patients with elevated intraocular pressure. *Am J Ophthalmol* 2002; 134(6): 863-71.

61. Kampik A, Arias-Puente A, O'Brart DP, Vuori ML, European Latanoprost Study G. Intraocular pressure-lowering effects of latanoprost and brimonidine therapy in patients with open-angle glaucoma or ocular hypertension: a randomized observer-masked multicenter study. *J Glaucoma* 2002; 11(2): 90-6.

62. Nordmann JP, Mertz B, Yannoulis NC, et al. A double-masked randomized comparison of the efficacy and safety of unoprostone with timolol and betaxolol in patients with primary open-angle glaucoma including pseudoexfoliation glaucoma or ocular hypertension. 6 month data. *Am J Ophthalmol* 2002; 133(1): 1-10.

63. Pfeiffer N, European Latanoprost Fixed Combination Study G. A comparison of the fixed combination of latanoprost and timolol with its individual components. *Graefes Arch Clin Exp Ophthalmol* 2002; 240(11): 893-9.

64. Simmons ST, Earl ML, Alphagan/Xalatan Study G. Three-month comparison of brimonidine and latanoprost as adjunctive therapy in glaucoma and ocular hypertension patients uncontrolled on beta-blockers: tolerance and peak intraocular pressure lowering. *Ophthalmology* 2002; 109(2): 307-14; discussion 14-5.

65. Sponsel WE, Paris G, Trigo Y, Pena M. Comparative effects of latanoprost (Xalatan) and unoprostone (Rescula) in patients with open-angle glaucoma and suspected glaucoma. *Am J Ophthalmol* 2002; 134(4): 552-9.

66. Tsukamoto H, Mishima HK, Kitazawa Y, et al. A comparative clinical study of latanoprost and isopropyl unoprostone in Japanese patients with primary open-angle glaucoma and ocular hypertension. *J Glaucoma* 2002; 11(6): 497-501.

67. Camras CB, Hedman K, Group USLS. Rate of response to latanoprost or timolol in patients with ocular hypertension or glaucoma. *J Glaucoma* 2003; 12(6): 466-9.

68. Cardascia N, Vetrugno M, Trabucco T, Cantatore F, Sborgia C. Effects of travoprost eye drops on intraocular pressure and pulsatile ocular blood flow: a 180-day, randomized, double-masked comparison with

latanoprost eye drops in patients with open-angle glaucoma. *Current therapeutic research, clinical and experimental* 2003; 64(7): 389-400.

69. Inan UU, Ermis SS, Yucel A, Ozturk F. The effects of latanoprost and brimonidine on blood flow velocity of the retrobulbar vessels: a 3-month clinical trial. *Acta Ophthalmol Scand* 2003; 81(2): 155-60.

70. Kamal D, Garway-Heath D, Ruben S, et al. Results of the betaxolol versus placebo treatment trial in ocular hypertension. *Graefes Arch Clin Exp Ophthalmol* 2003; 241(3): 196-203.

71. Parrish RK, Palmberg P, Sheu WP, Group XLTS. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. *Am J Ophthalmol* 2003; 135(5): 688-703.

72. Erkin EF, Tarhan S, Kayikcioglu OR, Deveci H, Guler C, Goktan C. Effects of betaxolol and latanoprost on ocular blood flow and visual fields in patients with primary open-angle glaucoma. *Eur J Ophthalmol* 2004; 14(3): 211-9.

73. Kobayashi H, Iwakiri R, Kobayashi K, Okinami S. Hypotensive effect of unoprostone as adjunct to latanoprost during multiple drug therapy for glaucoma. *Japanese Journal of Clinical Ophthalmology* 2004; 58(2): 193-7.

74. Vetrugno M, Cardascia N, Cantatore F, Sborgia C. Comparison of the effects of bimatoprost and timolol on intraocular pressure and pulsatile ocular blood flow in patients with primary open-angle glaucoma: A prospective, open-label, randomized, two-arm, parallel-group study. *Current therapeutic research, clinical and experimental* 2004; 65(6): 444-54.

75. Walters TR, DuBiner HB, Carpenter SP, Khan B, VanDenburgh AM, Bimatoprost Circadian IOPSG. 24-Hour IOP control with once-daily bimatoprost, timolol gel-forming solution, or latanoprost: a 1-month, randomized, comparative clinical trial. *Surv Ophthalmol* 2004; 49 Suppl 1: S26-35.

76. Wang TH, Huang JY, Hung PT, Shieh JW, Chen YF. Ocular hypotensive effect and safety of brinzolamide ophthalmic solution in open angle glaucoma patients. *J Formos Med Assoc* 2004; 103(5): 369-73.

77. Barnebey HS, Orengo-Nania S, Flowers BE, et al. The safety and efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution. *Am J Ophthalmol* 2005; 140(1): 1-7.

78. Camras CB, Sheu WP, United States Latanoprost-Brimonidine Study G. Latanoprost or brimonidine as treatment for elevated intraocular pressure: multicenter trial in the United States. *J Glaucoma* 2005; 14(2): 161-7.

79. Miglior S, Zeyen T, Pfeiffer N, et al. Results of the European Glaucoma Prevention Study. *Ophthalmology* 2005; 112(3): 366-75.

80. Erkin EF, Celik P, Kayikcioglu O, Deveci HM, Sakar A. Effects of latanoprost and betaxolol on cardiovascular and respiratory status of newly diagnosed glaucoma patients. *Ophthalmologica* 2006; 220(5): 332-7.

81. Koz OG, Ozsoy A, Yarangumeli A, Kose SK, Kural G. Comparison of the effects of travoprost, latanoprost and bimatoprost on ocular circulation: a 6-month clinical trial. *Acta Ophthalmol Scand* 2007; 85(8): 838-43.

82. Martin E, Martinez-de-la-Casa JM, Garcia-Feijoo J, Troyano J, Larrosa JM, Garcia-Sanchez J. A 6-month assessment of bimatoprost 0.03% vs timolol maleate 0.5%: hypotensive efficacy, macular thickness and flare in ocular-hypertensive and glaucoma patients. *Eye (Lond)* 2007; 21(2): 164-8.

83. Alagoz G, Gurel K, Bayer A, Serin D, Celebi S, Kukner S. A comparative study of bimatoprost and travoprost: effect on intraocular pressure and ocular circulation in newly diagnosed glaucoma patients. *Ophthalmologica* 2008; 222(2): 88-95.

84. Brandt JD, Cantor LB, Katz LJ, et al. Bimatoprost/timolol fixed combination: a 3-month double-masked, randomized parallel comparison to its individual components in patients with glaucoma or ocular hypertension. *J Glaucoma* 2008; 17(3): 211-6.

85. Kaback M, Scoper SV, Arzeno G, et al. Intraocular pressure-lowering efficacy of brinzolamide 1%/timolol 0.5% fixed combination compared with brinzolamide 1% and timolol 0.5%. *Ophthalmology* 2008; 115(10): 1728-34, 34 e1-2.

86. Williams RD, Cohen JS, Gross RL, et al. Long-term efficacy and safety of bimatoprost for intraocular pressure lowering in glaucoma and ocular hypertension: year 4. *Br J Ophthalmol* 2008; 92(10): 1387-92.

87. Yildirim N, Sahin A, Gultekin S. The effect of latanoprost, bimatoprost, and travoprost on circadian variation of intraocular pressure in patients with open-angle glaucoma. *J Glaucoma* 2008; 17(1): 36-9.

88. Casson RJ, Liu L, Graham SL, et al. Efficacy and safety of bimatoprost as replacement for latanoprost in patients with glaucoma or ocular hypertension: a uniocular switch study. *Journal of glaucoma* 2009; 18(8): 582-8.

89. Prata TS, Piassi MV, Melo LA, Jr. Changes in visual function after intraocular pressure reduction using antiglaucoma medications. *Eye (Lond)* 2009; 23(5): 1081-5.

90. Sharma R, Kohli K, Kapoor B, Mengi RK, Sadhotra P. The cardio-vascular effects of topical timolol, levobunolol and betaxolol in patients

of chronic simple glaucoma. *Journal of Clinical and Diagnostic Research* 2009; 3(4): 1615-20.

91. Zhao WJ. [Comparison of travoprost and timolol in patients with primary open angle glaucoma and ocular hypertension]. *International Journal of Ophthalmology* 2009; 9(9): 1753-4.

92. Birt CM, Buys YM, Ahmed, II, Trope GE. Prostaglandin efficacy and safety study undertaken by race (the PRESSURE study). *Journal of glaucoma* 2010; 19(7): 460-7.

93. Craven ER, Liu CC, Batoosingh A, Schiffman RM, Whitcup SM. A randomized, controlled comparison of macroscopic conjunctival hyperemia in patients treated with bimatoprost 0.01% or vehicle who were previously controlled on latanoprost. *Clin Ophthalmol* 2010; 4: 1433-40.

94. Higginbotham EJ, Olander KW, Kim EE, Grunden JW, Kwok KK, Tressler CS. Fixed combination of latanoprost and timolol vs individual components for primary open-angle glaucoma or ocular hypertension: a randomized, double-masked study. *Archives of ophthalmology* 2010; 128(2): 165-72.

95. Kammer JA, Katzman B, Ackerman SL, Hollander DA. Efficacy and tolerability of bimatoprost versus travoprost in patients previously on latanoprost: a 3-month, randomised, masked-evaluator, multicentre study. *The British journal of ophthalmology* 2010; 94(1): 74-9.

96. Macky TA. Bimatoprost versus travoprost in an Egyptian population: a hospital-based prospective, randomized study. *Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics* 2010; 26(6): 605-10.

97. Traverso CE, Ropo A, Papadia M, Uusitalo H. A phase II study on the duration and stability of the intraocular pressure-lowering effect and tolerability of Tafluprost compared with latanoprost. *Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics* 2010; 26(1): 97-104.

98. Nie X, Yang XH, Qin XF, Quan CJ, Yang SS. Correlation between the development of high myopia and intraocular pressure. *International Journal of Ophthalmology* 2011; 11(6): 1092-4.

99. Zhao L, Wang YL, Meng ZY, Hong H. Efficacy and safety of domestic Latanoprost in treating with open angle glaucoma and ocular hypertension. [Chinese]. *International Journal of Ophthalmology* 2011; 11(11): 1973-5.

100. Araie M, Yamazaki Y, Sugiyama K, Kuwayama Y, Tanihara H. [Phase III clinical trial of brimonidine in patients with primary open-angle glaucoma and ocular hypertension--comparison of the effects of brimonidine monotherapy versus timolol monotherapy, or combination

brimonidine/prostaglandins therapy versus combination placebo/prostaglandins therapy]. *Nippon Ganka Gakkai Zasshi - Acta Societatis Ophthalmologicae Japonicae* 2012; 116(10): 955-66.

101. Chabi A, Varma R, Tsai JC, et al. Randomized clinical trial of the efficacy and safety of preservative-free tafluprost and timolol in patients with open-angle glaucoma or ocular hypertension. *American journal of ophthalmology* 2012; 153(6): 1187-96.
102. Crichton AC, Vold S, Williams JM, Hollander DA. Ocular surface tolerability of prostaglandin analogs and prostamides in patients with glaucoma or ocular hypertension. *Advances in Therapy* 2013; 30(3): 260-70.
103. Delval L, Baudouin C, Gabisson P, Alliot E, Vincent B. Safety and efficacy of unpreserved timolol 0.1% gel in patients controlled by preserved latanoprost with signs of ocular intolerance. *Journal français d'ophtalmologie* 2013; 36(4): 316-23.
104. Katz G, Dubiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. *JAMA Ophthalmology* 2013; 131(6): 724-30.
105. Nguyen QH, McMenemy MG, Realini T, Whitson JT, Goode SM. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. *Journal of Ocular Pharmacology and Therapeutics* 2013; 29(3): 290-7.

Appendix III. Characteristics of included studies

			Eligibility criteria of included trials																
Reference	Year	Meta-analysis time points study included in	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age, years	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of followup, months	Types of analysis
1	1983	1991	Included	Included	NA	Excluded	NA	>=26 in both eyes	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	1	NR
2	1984	1991	Included	NA	NA	NA	Included	elevated IOPs	NR	Excluded	NA	Excluded	Yes	Yes	Multi (2)	United States	6	Other
3	1985	1991	Included	Included	NA	NA	NA	NR	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	3	NR
4	1985	1991	Included	Included	NA	NA	NA	>=23 in each eye?	>=18	Excluded	NA	Excluded	Yes	Yes	Can't tell	NR	15	NR
5	1985	1991	Included	Included	NA	NA	NA	>=23	NR	Excluded	NA	Excluded	Yes	Yes	Can't tell	NR	15	NR
6	1985	1991	Included	Included	NA	NA	NA	>=23 in each eye	NR	NA	NA	NA	Yes	Yes	Multi (NR)	NR	12	NR
7	1985	1991	Included	Included	NA	NA	NA	>=23 in each eye	NR	Excluded	NA	NA	Yes	Yes	Can't tell	NR	12	NR
8	1986	1991	Included	NA	NA	NA	NA	>=26 in at least one eye	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	6	NR
9	1988	1991	Included	Included	NA	NA	NA	NR	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	12	NR
10	1988	1991	Included	Included	NA	NA	NA	average measurement >25.5 and no measurement <22	adults	Excluded	Excluded	Excluded	Yes	Yes	Multi (3)	United States	6	Responders
11	1988	1991	NA	Included	Excluded	NA	NA	>=22	NR	NA	NA	NA	Yes	Yes	Single	NR	3	Evaluable population; Safety population or safety analysis
12	1988	1991	Included	Included	NA	NA	Included	>=22 in at least one eye?	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	3	NR
13	1988	1991	Included	Included	NA	NA	NA	>=21	NR	NA	NA	NA	Yes	Yes	Multi (2)	Canada	3	NR
14	1989	1991	NA	Included	NA	NA	NA	>=22 and <=28 in at least one eye	NR	Excluded	NA	Excluded	No	No	Single	United States	60	Intention-to-treat; Other
15	1989	1991	NA	Included	NA	NA	NA	>24 and <35, and difference between two eyes <=3	>=40	Excluded	Excluded	Excluded	Can't tell	No	Multi (2)	United States	61	NR
16	1989	1991	Included	Included	NA	Excluded	Excluded	>=24	>=18	Excluded	Excluded	Excluded	Yes	Yes	Multi (16)	Japan	3	NR
17	1991	1991	NA	Included	NA	NA	NA	>=22	>=45 and <=70	Excluded	NA	Excluded	Can't tell	No	Can't tell	NR	73	Intention-to-treat; Other
18	1991	1991	Included	Included	NA	NA	NA	exclude patients whose increased IOP was not controlled by a single-drug therapy	NR	NA	NA	NA	Yes	Yes	Multi (NR)	NR	3	Other
19	1992	1991, 1995	Can't tell	Included	NA	NA	Excluded	NR	NR	Excluded	Excluded	NA	Yes	Yes	Multi (7)	NR	2	NR
20	1992	1991, 1995	Included	NA	NA	NA	NA	>21	>=18 and <=80	Excluded	Excluded	Excluded	Yes	Yes	Multi (NR)	NR	12	Compliers or Adheres
21	1993	1991, 1995	Included	Included	Excluded	Excluded	Excluded	>=22 and <=35	NR	Excluded	NA	Excluded	Yes	Yes	Multi (18)	Japan	3	NR
22	1993	1991, 1995	Included	Included	NA	NA	NA	NR	>=21	Excluded	Excluded	Excluded	Yes	Yes	Multi (NR)	NR	3	NR
23	1993	1991, 1995	Included	Included	NA	NA	NA	NR	NR	Excluded	NA	Excluded	Yes	Yes	Multi (3)	United States	1	Per protocol
24	1994	1991, 1995	Included	Included	NA	NA	Included	>=22	NR	NA	NA	NA	Yes	Yes	Multi (NR)	NR	3	NR
25	1994	1991, 1995	Included	Included	NA	NA	NA	>=21 and <30 in each eye	>=20 and <=70	Excluded	Excluded	Excluded	Yes	Yes	Multi (51)	Japan	3	NR
26	1994	1991, 1995	NA	Included	NA	NA	NA	>=22 and <=30	NR	NA	NA	NA	Can't tell	No	Can't tell	NR	24	NR
27	1995	1991, 1995	Included	Included	NA	Excluded	Included	>=22	>=40	Excluded	Excluded	Excluded	Yes	Yes	Multi (13)	Sweden; Denmark; Finland; Norway	6	NR
28	1995	1991, 1995	NA	Included	NA	NA	NA	>=21 and <35	NR	Excluded	Excluded	Excluded	Can't tell	No	Single	United States	24	NR

			Eligibility criteria of included trials															
Reference	Year	Meta-analysis time points study included in	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age, years	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of followup, months	Types of analysis
29	1995	1991, 1995	Included	Included	NA	NA	NA	>=23	>=21 and <=85	Excluded	NA	Excluded	Yes	Yes	Multi (34)	Costa Rica; Colombia; United States; Mexico; United Kingdom; Switzerland; France; Austria; Australia; Holland; Germany; Peru; Brazil; Israel; Belgium; Argentina; Canada; Sweden; Portugal; New Zealand; Iceland	12	Intention-to-treat; Per protocol
30	1996	1991, 1995, 2002	Included	Included	NA	Excluded	Included	>=22	>40	Excluded	Excluded	Excluded	Yes	Yes	Multi (NR)	Sweden	6	NR
31	1996	1991, 1995, 2002	Included	Included	NA	NA	NA	NR	NR	Excluded	Excluded	Excluded	No	Yes	Multi (35)	Japan	3	NR
32	1996	1991, 1995, 2002	Included	Included	NA	NA	NA	post-washout IOP >=25 mmHg and <35 mmHg in each eye, excluded IOP asymmetry of more than 5 mmHg	adults	Excluded	Excluded	Excluded	Yes	Yes	Multi (NR)	NR	12	Safety population or safety analysis
33	1996	1991, 1995, 2002	Included	Included	NA	NA	NA	>=22 and <=34, and difference between two eyes <=5	>=21	Excluded	Excluded	Excluded	Yes	Yes	Multi (13)	United States	3	Per protocol; Safety population or safety analysis
34	1996	1991, 1995, 2002	Included	Included	NA	NA	NA	>=22 and <=35, and difference between two eyes <=4	adults	Excluded	Excluded	Excluded	Yes	Yes	Multi (16)	United States	3	NR
35	1996	1991, 1995, 2002	Included	Included	NA	Excluded	Included	>=22	>=40	Excluded	Excluded	Excluded	Yes	Yes	Multi (14)	United Kingdom	6	NR
36	1996	1991, 1995, 2002	Included	Included	NA	NA	NA	NR	>=40 and <=70	Excluded	NA	Excluded	Yes	No	Multi (3)	Japan	4	NR
37	1997	1991, 1995, 2002	Included	Included	NA	NA	NA	<=20 in both eyes and difference between two eyes <=4, and IOP fluctuation between both eyes=<2 at baseline and 6 weeks prior to the study	>=20 and <=75	Excluded	Excluded	Excluded	Yes	No	Multi (24)	Japan	3	Intention-to-treat
38	1997	1991, 1995, 2002	Included	Included	NA	NA	Excluded	>=22 and <=34, and difference between two eyes <5	>=18 and <=85	Excluded	Excluded	NA	Yes	Yes	Multi (13)	United States	3	Intention-to-treat
39	1998	1991, 1995, 2002	Included	Included	NA	Excluded	NA	NR	>=21 and <=85	Excluded	Excluded	Excluded	No	Yes	Multi (27)	USA	3	Per protocol; Other
40	1998	1991, 1995, 2002	Included	Included	NA	Excluded	NA	>=22 at 9AM and 11AM	>=21	Excluded	Excluded	Excluded	Yes	No	Multi (22)	United States	3	Per protocol; Safety population or safety analysis; Other
41	1998	1991, 1995, 2002	Included	NA	NA	Excluded	Included	>=25 with IOP-reducing therapy or >=30 without IOP-reducing therapy	>=18	Excluded	Excluded	Excluded	Yes	No	Multi (13)	Germany	1	NR
42	1998	1991, 1995, 2002	Included	Included	NA	NA	Excluded	>=23 and <=35, and difference between two eyes <=5	>=21	Excluded	Excluded	Excluded	Yes	Yes	Multi (NR)	NR	12	Per protocol; Safety population or safety analysis
43	1998	1991, 1995, 2002	Included	Included	NA	Excluded	NA	>=23 in at least one eye?	>=21	Excluded	NA	Excluded	Yes	Yes	Multi (24)	United States	3	Per protocol; At least receiving one treatment

			Eligibility criteria of included trials															
Reference	Year	Meta-analysis time points study included in	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age, years	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of followup, months	Types of analysis
44	1998	1991, 1995, 2002	Included	Included	Excluded	Excluded	Included	NR	>=21	Excluded	Excluded	Excluded	Yes	Yes	Multi (42)	United States; Germany; France; Belgium; Portugal; the Netherlands; Iceland	3	Intention-to-treat; Per protocol; Responders; At least receiving one treatment; Safety population or safety analysis
45	1999	1991, 1995, 2002	Included	NA	NA	NA	NA	NR	NR	NA	NA	NA	No	Yes	Can't tell	NR	3	NR
46	1999	1991, 1995, 2002	Included	Included	NA	NA	Excluded	NR	NR	Excluded	Excluded	Excluded	Yes	Yes	Multi (NR)	United States	3	Intention-to-treat
47	1999	1991, 1995, 2002	NA	Included	NA	NA	NA	>=20 and <=40	NR	Excluded	Excluded	Excluded	Yes	No	Single	United States	1	NR
48	2000	1991, 1995, 2002	Included	Included	NA	NA	Included	NR	>40	NA	NA	NA	Can't tell	No	Multi (13)	Sweden	6	NR
49	2000	1991, 1995, 2002	Included	Included	NA	Excluded	Included	NR	NR	Excluded	Excluded	Excluded	Yes	Yes	Multi (12)	NR	3	NR
50	2000	1991, 1995, 2002	Included	Included	Excluded	Excluded	Included	>=24 and <=36 at 8AM and >= 21 and <= 36 mmHg at 10AM and 6PM	>=21	Excluded	Excluded	Excluded	Yes	Yes	Multi (24)	United States	3	Intention-to-treat; Per protocol; Safety population or safety analysis
51	2001	1991, 1995, 2002	Included	Included	NA	Excluded	Included	>=21	NR	Excluded	Excluded	Excluded	Yes	Yes	Multi (NR)	France	1	NR
52	2001	1991, 1995, 2002	Included	Included	NA	NA	NA	>=22 and <=34	>=18	Excluded	Excluded	Can't tell	Yes	Yes	Multi (5)	United states	3	Per protocol
53	2001	1991, 1995, 2002	NA	Included	NA	NA	NA	>=21 and <=29 in each eye	>=20 and <=79	Excluded	Excluded	Excluded	No	No	Can't tell	NR	2	Safety population or safety analysis; Other
54	2001	1991, 1995, 2002	Included	Included	NA	Excluded	NA	>=21	>=18	Excluded	Excluded	Excluded	Yes	Yes	Single	Brazil	2	Intention-to-treat; Per protocol
55	2002	1991, 1995, 2002	Included	Included	NA	Excluded	Excluded	>21	>=21	Excluded	Excluded	Excluded	No	No	Multi (2)	Singapore	2	NR
56	2002	1991, 1995, 2002	Included	NA	NA	Included	NA	excluded mean IOP of two eyes >30 or any IOP >35 in one eye	NR	Excluded	Excluded	Excluded	No	No	Single	Sweden	1	Intention-to-treat
57	2002	1991, 1995, 2002	Included	NA	NA	NA	NA	NR	NR	NA	NA	NA	Can't tell	Can't tell	Can't tell	NR	12	NR
58	2002	1991, 1995, 2002	Included	Included	NA	NA	Included	>=24 and <=36	>=21	Excluded	Excluded	Excluded	Yes	Yes	Multi (44)	United States	6	Intention-to-treat; Per protocol; Safety population or safety analysis
59	2002	1991, 1995, 2002	Included	Included	NA	Excluded	Included	>=25 with IOP-reducing therapy or >=30 without IOP-reducing therapy	>=18	Excluded	Excluded	Excluded	Yes	No	Multi (38)	United States	12	Intention-to-treat; Safety population or safety analysis
60	2002	1991, 1995, 2002	Included	Included	NA	Excluded	NA	>=21	>=18	Excluded	Excluded	Excluded	Yes	Yes	Multi (24)	United States	2	Intention-to-treat; Safety population or safety analysis
61	2002	1991, 1995, 2002	Included	Included	NA	Excluded	Included	NR	NR	Excluded	Excluded	Excluded	Yes	Yes	Multi (30)	Germany; United Kingdom; Spain; Finland	6	Intention-to-treat
62	2002	1991, 1995, 2002	Included	Included	NA	NA	Included	NR	adults	Excluded	Excluded	Excluded	Yes	Yes	Multi (27)	Europe; Israel	24	Intention-to-treat
63	2002	1991, 1995, 2002	Included	Included	NA	Excluded	Included	>=25 with IOP-reducing therapy or >=30 without IOP-reducing therapy	>=18	Excluded	Excluded	Excluded	Yes	No	Multi (37)	NR	6	Intention-to-treat; At least receiving one treatment
64	2002	1991, 1995, 2002	Included	Included	NA	NA	NA	>=18 and <=34, and difference between two eyes <=5	>=21	NA	NA	NA	Yes	No	Multi (14)	United States	3	NR
65	2002	1991, 1995, 2002	Included	Included	NA	Excluded	NA	>=21 and <=27, and difference between two eyes <2	>=18	Excluded	NA	Excluded	Yes	Yes	Single	United States	1	NR

			Eligibility criteria of included trials															
Reference	Year	Meta-analysis time points study included in	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age, years	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of followup, months	Types of analysis
66	2002	1991, 1995, 2002	NA	NA	NA	NA	NA	>=21 and <=30	NR	Excluded	NA	Excluded	Yes	Yes	Multi (10)	Japan	2	NR
67	2003	1991, 1995, 2002, 2004	Included	Included	Can't tell	Can't tell	Can't tell	NR	NR	Can't tell	Can't tell	Can't tell	Yes	Yes	Multi (17)	United States	6	Intention-to-treat; Responders
68	2003	1991, 1995, 2002, 2004	Included	NA	Excluded	Excluded	Excluded	>20	>=40 and <=60	NA	NA	NA	No	No	Single	Italy	6	NR
69	2003	1991, 1995, 2002, 2004	Included	Included	NA	NA	NA	NR	NR	Excluded	Excluded	Excluded	Yes	Yes	Can't tell	NR	3	NR
70	2003	1991, 1995, 2002, 2004	NA	Included	NA	NA	NA	>=22 and <=35	>35	NA	NA	NA	Can't tell	No	Single	United Kingdom	37	Intention-to-treat
71	2003	1991, 1995, 2002, 2004	Included	Included	NA	Excluded	Included	>=21	>=18	Excluded	Excluded	Excluded	Yes	Yes	Multi (45)	United States	3	Intention-to-treat; Per protocol; Safety population or safety analysis
72	2004	1991, 1995, 2002, 2004	Included	NA	NA	NA	NA	NR	NR	Excluded	NA	Excluded	No	No	Can't tell	NR	3	NR
73	2004	1991, 1995, 2002, 2004	Included	NA	NA	NA	NA	NR	NR	NA	NA	NA	Yes	No	Single	NR	2	NR
74	2004	1991, 1995, 2002, 2004	Included	Included	Excluded	Excluded	Excluded	<16 on timolol for 12 months	>=40 and <=60	NA	NA	NA	Can't tell	No	Single	Italy	6	NR
75	2004	1991, 1995, 2002, 2004	Included	Included	NA	NA	NA	>=22 and <=34, and difference between two eyes <=5	adults	Excluded	Excluded	Excluded	Yes	Yes	Multi (7)	United States	1	Intention-to-treat; Modified intention-to-treat; Safety population or safety analysis
76	2004	1991, 1995, 2002, 2004	Included	NA	NA	Excluded	NA	>=20 and <=30	NR	NA	NA	NA	Yes	Yes	Single	Taiwan	1	NR
77	2005	1991, 1995, 2002, 2004, 2009	Included	Included	Excluded	Excluded	Excluded	NR	>=18	Excluded	Excluded	Excluded	Yes	Yes	Multi (33)	United States	3	Intention-to-treat
78	2005	1991, 1995, 2002, 2004, 2009	Included	Included	NA	Excluded	NA	>=22	>=18	Excluded	Excluded	Excluded	Yes	Yes	Multi (23)	United States	6	Intention-to-treat; Per protocol; Safety population or safety analysis
79	2005	1991, 1995, 2002, 2004, 2009	NA	Included	NA	NA	NA	>=22 and <=29 in at least one eye?	>=30 and <=80	Excluded	NA	Excluded	Yes	Yes	Multi (18)	Belgium; Germany; Italy; Portugal	61	Intention-to-treat; Safety population or safety analysis
80	2006	1991, 1995, 2002, 2004, 2009	Included	NA	NA	NA	NA	NR	NR	Excluded	Excluded	Excluded	No	No	Can't tell	NR	3	NR
81	2007	1991, 1995, 2002, 2004, 2009	Included	Included	NA	NA	NA	>=22 and <=36	>=18	Excluded	Excluded	Excluded	No	No	Can't tell	NR	6	Other
82	2007	1991, 1995, 2002, 2004, 2009	Included	Included	NA	NA	Included	>=24 and <=34	>18	Excluded	Excluded	Excluded	Yes	Yes	Can't tell	Spain	6	NR
83	2008	1991, 1995, 2002, 2004, 2009	Included	NA	NA	NA	Included	<=36	>=18	Excluded	Excluded	Excluded	No	No	Single	Turkey	6	NR
84	2008	1991, 1995, 2002, 2004, 2009	Included	Included	NA	Included	NA	>=18 with IOP-reducing medication or >=24 for treatment naive patients in at least one eye	adults	Excluded	Excluded	Excluded	Yes	Yes	Multi (59)	United States; Canada	3	Intention-to-treat
85	2008	1991, 1995, 2002, 2004, 2009	Included	Included	NA	Excluded	Included	>=18 at 8AM or >=21 at 10AM and <=36 in at least one eye	>=18	Excluded	Excluded	Excluded	Yes	Yes	Multi (35)	United States	6	Intention-to-treat; Per protocol

			Eligibility criteria of included trials															
Reference	Year	Meta-analysis time points study included in	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age, years	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of followup, months	Types of analysis
86	2008	1991, 1995, 2002, 2004, 2009	Can't tell	Included	Can't tell	Can't tell	Can't tell	>=22 and <=34	NR	NA	NA	NA	Yes	Yes	Multi (15)	United States	49	Intention-to-treat; Per protocol; At least receiving one treatment; Safety population or safety analysis
87	2008	1991, 1995, 2002, 2004, 2009	Included	NA	NA	Excluded	NA	>22	>=18	Excluded	NA	Excluded	No	No	Can't tell	NR	2	NR
88	2009	1991, 1995, 2002, 2004, 2009	Can't tell	Included	Can't tell	Can't tell	Can't tell	>=17 and <=22 in each eye	>=18	Excluded	NA	Excluded	Yes	No	Multi (8)	Australia	6	Intention-to-treat; Safety population or safety analysis
89	2009	1991, 1995, 2002, 2004, 2009	Included	NA	NA	NA	Excluded	>21	NR	NA	NA	NA	Yes	No	Single	Brazil	1	NR
90	2009	1991, 1995, 2002, 2004, 2009	Included	NA	Included	NA	NA	NR	>=40 and <=80	Excluded	NA	Excluded	Yes	No	Single	India	3	NR
91	2009	1991, 1995, 2002, 2004, 2009	Included	Included	NA	NA	NA	>=22	>=18 and <=70	Excluded	Excluded	Excluded	Yes	SUBVALUE()	Can't tell	China	3	NR
92	2010	1991, 1995, 2002, 2004, 2009, 2014	Included	Included	NA	NA	Included	>23 and <36	NR	Excluded	Excluded	Excluded	Yes	Yes	Multi (9)	Canada	6	Per protocol
93	2010	1991, 1995, 2002, 2004, 2009, 2014	NA	Included	NA	NA	NA	difference between two eyes <=5	>=18	Excluded	Excluded	NA	Yes	No	Multi (15)	United States	1	Modified intention-to-treat
94	2010	1991, 1995, 2002, 2004, 2009, 2014	Included	Included	NA	Excluded	Included	>=26 and <=36	>=18	Excluded	Excluded	Excluded	Yes	Yes	Multi (58)	United States	3	Intention-to-treat; At least receiving one treatment; Eligible population; Safety population or safety analysis
95	2010	1991, 1995, 2002, 2004, 2009, 2014	Can't tell	Included	Can't tell	Can't tell	Can't tell	inadequate IOP control after at least 30 days on latanoprost monotherapy, judged by the investigator	adults	Excluded	NA	Excluded	Yes	No	Multi (17)	NR	3	Intention-to-treat
96	2010	1991, 1995, 2002, 2004, 2009, 2014	Included	Included	Excluded	Excluded	Can't tell	>=21 and <=35 in each eye	>=18	Excluded	NA	Excluded	Yes	Yes	Multi (NR)	Egypt	6	NR
97	2010	1991, 1995, 2002, 2004, 2009, 2014	Included	Included	NA	NA	Included	>=22 and <=34 in at least one eye	>=18	Excluded	NA	Excluded	Yes	Yes	Multi (3)	Italy; Finland	1	Intention-to-treat; At least receiving one treatment; Safety population or safety analysis
98	2011	1991, 1995, 2002, 2004, 2009, 2014	NA	NA	NA	NA	NA	NR	NR	NA	NA	NA	Can't tell	No	Single	China	27	NR
99	2011	1991, 1995, 2002, 2004, 2009, 2014	Included	Included	NA	Excluded	Excluded	>=21 and <=35 if not controlled, or <=21 on beta-blocker monotherapy	NR	Can't tell	Excluded	Can't tell	Yes	Yes	Single	China	1	NR

			Eligibility criteria of included trials															
Reference	Year	Meta-analysis time points study included in	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age, years	Prior gluacoma surgery	Prior glaucoma laser	Prior cataract surgery	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of followup, months	Types of analysis
100	2012	1991, 1995, 2002, 2004, 2009, 2014	Included	Included	NA	NA	NA	=<31 in both eyes; >=18 for POAG patients; >=22 for OHT patients	>=20	Excluded	NA	Excluded	Yes	Yes	Multi (51)	Japan	1	At least receiving one treatment; Safety population or safety analysis
101	2012	1991, 1995, 2002, 2004, 2009, 2014	Included	Included	NA	NA	Included	>=23 and <=36, and difference between two eyes <5	>=18	Excluded	NA	Excluded	Yes	Yes	Multi (50)	United States; Spain; Switzerland	3	Per protocol; At least receiving one treatment
102	2013	1991, 1995, 2002, 2004, 2009, 2014	Included	Included	NA	NA	NA	NR	>=18	Excluded	NA	NA	Yes	Yes	Multi (15)	Canada; United States	3	Intention-to-treat; Per protocol; Safety population or safety analysis
103	2013	1991, 1995, 2002, 2004, 2009, 2014	Included	Included	Excluded	Excluded	Excluded	<=18	>=18 and <=90	NA	NA	NA	Yes	No	Multi (45)	France	3	Per protocol; Other
104	2013	1991, 1995, 2002, 2004, 2009, 2014	Included	Included	Excluded	Excluded	Excluded	>=24 and <=36 at 8AM and >=21 and <=36 at 10AM; <36 in both eyes at all time points	>=18	Excluded	Excluded	Excluded	Yes	Yes	Multi (66)	United States	3	Intention-to-treat; Safety population or safety analysis
105	2013	1991, 1995, 2002, 2004, 2009, 2014	Included	Included	NA	Excluded	NA	>=24 and <=36 at 8AM and >=21 and <=36 at 10AM; <36 in both eyes at all time points	>=18	Excluded	Excluded	Excluded	Yes	Yes	Multi (65)	United States	6	Intention-to-treat; Safety population or safety analysis

NA: Not Applicable
NR: Not Reported
IOP: Intraocular pressure

Appendix IV. Risk of bias table

Reference	Year	Network meta-analysis time points study included in	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
1	1983	1991	NR	NR	NR/CT	NR/CT	Yes	Yes	No
2	1984	1991	Randomly numbered with a unique code by a third party	Each patient, in sequence, was assigned a study number corresponding to a test drug…The code was broken at the end of the study	Yes	Yes	No	NR	No
3	1985	1991	NR	NR	NR/CT	NR/CT	Yes	Yes	Yes
4	1985	1991	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
5	1985	1991	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
6	1985	1991	NR	NR	NR/CT	NR/CT	Yes	NR	No
7	1985	1991	NR	NR	Yes	NR/CT	Yes	NR	No
8	1986	1991	NR	NR	Yes	NR/CT	Yes	Yes	Yes
9	1988	1991	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
10	1988	1991	NR	Patients were then randomly assigned in a double-masked fashion to one of two treatment groups	NR/CT	NR/CT	Yes	Yes	No
11	1988	1991	NR	NR	Yes	NR/CT	Yes	NR	No
12	1988	1991	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
13	1988	1991	NR	NR	Yes	Yes	No	NR	No
14	1989	1991	The treatment assignment was done in stratified groups based on the patient's baseline IOP and the number of eyes which were entered in the study	The randomization list was kept by the research secretary, and the examining physician did not know to which group a newly recruited patient would be assigned	No	Yes	No	Yes	No
15	1989	1991	NR	NR	NR/CT	NR/CT	Yes	Yes	No
16	1989	1991	NR	The randomization list was kept by each controller until the end of the study	NR/CT	NR/CT	Yes	NR	No
17	1991	1991	NR	NR	No	NR/CT	No	Yes	No
18	1991	1991	NR	NR	Yes	NR/CT	Yes	NR	No
19	1992	1991, 1995	NR	NR	Yes	NR/CT	No	NR	Yes
20	1992	1991, 1995	Participating patients were distributed randomly, i.e. each new patient entering the study received the next-numbered, masked bottle	Participating patients were distributed randomly, i.e. each new patient entering the study received the next-numbered, masked bottle	NR/CT	NR/CT	Yes	Yes	No
21	1993	1991, 1995	The containers were confirmed as indistinguishable, and allotted in a randomized manner by the controller. The key code table was retained by the controller	The containers were confirmed as indistinguishable, and allotted in a randomized manner by the controller. The key code table was retained by the controller	Yes	NR/CT	Yes	NR	No
22	1993	1991, 1995	NR	NR	Yes	NR/CT	Yes	Yes	Yes
23	1993	1991, 1995	NR	NR	NR/CT	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
24	1994	1991, 1995	NR	NR	NR/CT	NR/CT	Yes	Yes	Yes
25	1994	1991, 1995	NR	NR	No	NR/CT	No	NR	No
26	1994	1991, 1995	NR	NR	NR/CT	NR/CT	No	NR	No
27	1995	1991, 1995	The patients were allocated to treatment groups according to a computer-generated scheme prepared by Pharmacia	NR	Yes	NR/CT	Yes	Yes	Yes

Reference	Year	Network meta-analysis time points study included in	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
28	1995	1991, 1995	Subjects were then placed on either placebo or timolol drops in both eyes twice a day in a double masked manner using randomized number tables.	NR	Yes	Yes	No	Yes	Yes
29	1995	1991, 1995	NR	NR	Yes	NR/CT	Yes	Yes	Yes
30	1996	1991, 1995, 2002	NR	NR	NR/CT	NR/CT	Yes	Yes	No
31	1996	1991, 1995, 2002	NR	NR	Yes	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
32	1996	1991, 1995, 2002	NR	NR	Yes	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
33	1996	1991, 1995, 2002	NR	NR	NR/CT	NR/CT	Yes	NR	No
34	1996	1991, 1995, 2002	NR	NR	Yes	NR/CT	Yes	Yes	Reported none of the authors has any financial relationship
35	1996	1991, 1995, 2002	The patients were allocated to different treatment groups according to a pregenerated randomization list.	NR	NR/CT	NR/CT	Yes	Yes	Yes
36	1996	1991, 1995, 2002	Envelope method	Envelope method	NR/CT	NR/CT	No	NR	Reported none of the authors has any financial relationship
37	1997	1991, 1995, 2002	NR	NR	NR/CT	NR/CT	Yes	NR	No
38	1997	1991, 1995, 2002	NR	NR	NR/CT	NR/CT	Yes	Yes	No
39	1998	1991, 1995, 2002	Patients with an IOP of greater than or equal to 24 mm Hg in at least one eye (the same eye) at hours 0 and 2 were then randomly assigned, according to a computer-generated allocation schedule.	NR	Yes	NR/CT	Yes	NR	Yes
40	1998	1991, 1995, 2002	Patients randomly (according to a computer-generated allocation schedule) received one of the following masked treatment regimens for 3 months	All study medication was packaged in identical bottles by allocation number	Yes	NR/CT	Yes	Yes	Yes
41	1998	1991, 1995, 2002	The patients were allocated to the treatment groups according to a computer-generated list prepared by Pharmacia & Upjohn (Uppsala, Sweden).	NR	NR/CT	NR/CT	Yes	Yes	Yes

Reference	Year	Network meta-analysis time points study included in	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
42	1998	1991, 1995, 2002	Randomization schedules were generated for each site using SAS (Version 6.08; SAS Institute, Cary, NC) procedure, PROC PLAN.	Patients were assigned sequentially to masked treatment according to a randomization schedule generated by the study sponsor (Allergan, Inc). Each bottle of test medication was coded with a shipment number and labeled with a study number. Each time a bottle was dispensed to a patient, the tearoff portion of the label was attached to the patient's case-report form.	Yes	Yes	No	Yes	Reported none of the authors has any financial relationship
43	1998	1991, 1995, 2002	NR	NR	Yes	NR/CT	Yes	Yes	Yes
44	1998	1991, 1995, 2002	Computer-generated randomization code	All clinical supplies were labeled based on a computer-generated randomization code and dispensed in numerical sequence to patients at each investigational site.	Yes	NR/CT	Yes	Yes	Yes
45	1999	1991, 1995, 2002	NR	NR	No	Yes	No	NR	No
46	1999	1991, 1995, 2002	NR	NR	NR/CT	NR/CT	Yes	Yes	No
47	1999	1991, 1995, 2002	NR	NR	NR/CT	NR/CT	Yes	NR	No
48	2000	1991, 1995, 2002	NR	NR	No	No	Yes	Yes	No
49	2000	1991, 1995, 2002	NR	NR	No	No	No	Yes	No
50	2000	1991, 1995, 2002	NR	NR	Yes	NR/CT	Yes	Yes	No
51	2001	1991, 1995, 2002	The randomization was stratified for centre and performed in blocks of six consecutive patients within each centre.	NR	NR/CT	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
52	2001	1991, 1995, 2002	NR	NR	Yes	NR/CT	Yes	Yes	Reported none of the authors has any financial relationship
53	2001	1991, 1995, 2002	Patients were randomized using computer-generated numbers (0 = receive latanoprost in the right eye and unoprostone in the left eye, 1 = receive unoprostone in the right eye and latanoprost in the left eye).	NR	No	Yes	No	NR	No
54	2001	1991, 1995, 2002	Patients were dispensed study medication that was packaged in identical bottles according to a computer-generated randomization list provided by Pharmacia & Upjohn, Sweden.	Patients were dispensed study medication that was packaged in identical bottles according to a computer-generated randomization list provided by Pharmacia & Upjohn, Sweden. Disclosure envelopes were kept in a locked cabinet at the study site. In the event of an emergency requiring identification of the masked treatment, the envelope could be opened. No envelopes were opened during the trial.	Yes	NR/CT	Yes	Yes	No

Reference	Year	Network meta-analysis time points study included in	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
55	2002	1991, 1995, 2002	On the baseline day, the patients were randomised (by block randomisation) to two parallel study groups	NR	No	Yes	No	No	Yes
56	2002	1991, 1995, 2002	The method used for preparing the allocation schedule was based on blocked randomization, in blocks of eight allocation numbers	Patients were assigned allocation numbers at the prestudy visit. Drops were contained in identical bottles marked with allocation numbers. During the study the assignment codes were kept in sealed envelopes in a locked space at the study location, and were delivered with unbroken seals on completion of trial	Yes	Yes	No	Yes	No
57	2002	1991, 1995, 2002	NR	NR	NR/CT	NR/CT	Yes	Yes	Yes
58	2002	1991, 1995, 2002	Patients who met all study eligibility criteria were assigned a patient number and sequentially randomly assigned to one of three treatment groups in an equal (1:1:1) ratio by means of a computergenerated randomization schedule prepared by the Alcon Biostatistics Department. Randomization was stratified by site to ensure balanced treatment within each site	Medication description was concealed from the patient, investigator, and clinical study staff. Masked medication was packaged in identical Drop-Tainers and provided to the investigators along with sealed envelopes containing the medication description for each patient.	Yes	Yes	No	Yes	Reported none of the authors has any financial relationship
59	2002	1991, 1995, 2002	Patients were allocated to 1 of 3 treatment groups according to a computer-generated randomization code list. A single block randomization list was generated for the entire study	Drug was issued according to patient numbers that were given in consecutive order at baseline. Medications were provided in identical coded bottles. Study medication was shipped to the individual study sites in sets such that each set was a multiple of the block size used in generating the randomization	NR/CT	NR/CT	Yes	Yes	No
60	2002	1991, 1995, 2002	Randomization codes were generated and medical supplies were prepared by Pharmacia clinical Supply Logistics (Kalamazoo, Michigan, USA).	Each center received prepackaged clinical supplies with patient numbers, which were allocated sequentially	No	NR/CT	No	Yes	Yes
61	2002	1991, 1995, 2002	NR	NR	NR/CT	NR/CT	Yes	Yes	No
62	2002	1991, 1995, 2002	Computer-generated randomization schedule	Medication identity was concealed in individually sealed envelopes stored at the study sites	Yes	NR/CT	Yes	Yes	No
63	2002	1991, 1995, 2002	NR	NR	Yes	NR/CT	Yes	Yes	Reported none of the authors has any financial relationship

Reference	Year	Network meta-analysis time points study included in	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
64	2002	1991, 1995, 2002	the randomization code was maintained at the central coordination center.	NR	Yes	NR/CT	Yes	Yes	No
65	2002	1991, 1995, 2002	NR	NR	No	NR/CT	Yes	Yes	Yes
66	2002	1991, 1995, 2002	Registration System controller randomly allocated patients into these two groups by assigning patients into blocks in sequence of registration to the center, which was determined by the investigators. Each block consisted of six patients for a set of treatments (three latanoprost, three unoprostone) where the order of treatments within the block had been randomized.	Registration System controller randomly allocated patients into these two groups by assigning patients into blocks in sequence of registration to the center, which was determined by the investigators. Each block consisted of six patients for a set of treatments (three latanoprost, three unoprostone) where the order of treatments within the block had been randomized.	NR/CT	NR/CT	NR/CT	NR	No
67	2003	1991, 1995, 2002, 2004	NR	NR	NR/CT	NR/CT	Yes	Yes	Yes
68	2003	1991, 1995, 2002, 2004	NR	NR	Yes	Yes	Yes	Yes	No
69	2003	1991, 1995, 2002, 2004	NR	NR	No	No	No	NR	Reported none of the authors has any financial relationship
70	2003	1991, 1995, 2002, 2004	The chief pharmacist at Moorfields Eye Hospital, who had no other direct involvement with the trial, randomised one of the patients in each pair to treatment with either betaxolol drops or placebo drops. The fellow member of the pair was then allocated to the alternative treatment arm. Randomisation was carried out by means of randomisation tables.	Each patient was assigned drops coded either A, B, C or D that corresponded to their trial number.	Yes	Yes	No	Yes	Reported none of the authors has any financial relationship
71	2003	1991, 1995, 2002, 2004	NR	NR	No	Yes	No	Yes	No
72	2004	1991, 1995, 2002, 2004	NR	NR	No	Yes	Yes	NR	No
73	2004	1991, 1995, 2002, 2004	NR	NR	NR/CT	NR/CT	No	NR	No
74	2004	1991, 1995, 2002, 2004	At the baseline visit (day 0), eligible patients were randomly assigned, using a computer-generated randomization code list, to 1 of 2 treatment groups.	NR	No	No	No	NR	No
75	2004	1991, 1995, 2002, 2004	The randomization schedule was generated using a SAS (version 6.12) program and stored in a locked cabinet until the study was completed.	The randomization schedule was generated using a SAS (version 6.12) program and stored in a locked cabinet until the study was completed.	No	No	Yes	Yes	Yes

Reference	Year	Network meta-analysis time points study included in	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
76	2004	1991, 1995, 2002, 2004	A computer-generated list of random assignments decided which treatment patients would receive	The list was sealed and could be opened only after the completion of the study protocol or after any serious adverse event occurred	NR/CT	NR/CT	Yes	NR	No
77	2005	1991, 1995, 2002, 2004, 2009	Computer generated	Assign patient numbers sequentially; opaque syndiotactic polypropylene oval bottles	Yes	NR/CT	Yes	Yes	No
78	2005	1991, 1995, 2002, 2004, 2009	Randomization was performed by centralized allocation by Voice Processing Plus, Inc., via an interactive phone registration system.	Randomization was performed by centralized allocation by Voice Processing Plus, Inc., via an interactive phone registration system.	NR/CT	Yes	No	Yes	Yes
79	2005	1991, 1995, 2002, 2004, 2009	Randomization was obtained at the Coordinating Center. Each clinical center had its own randomization list that was stratified for pseudoexfoliation, pigmentary dispersion syndrome, and diabetes mellitus.	[illegible] placebo were given to each center according to the randomization list. Patients were given a bottle marked with a code label. The allocation code was secured at the Coordinating Center at the office of the Project Coordinator.	Yes	Yes	No	Yes	No
80	2006	1991, 1995, 2002, 2004, 2009	NR	NR	NR/CT	NR/CT	Yes	NR	No
81	2007	1991, 1995, 2002, 2004, 2009	NR	NR	NR/CT	Yes	Yes	NR	No
82	2007	1991, 1995, 2002, 2004, 2009	NR	NR	NR/CT	Yes	No	No	Reported none of the authors has any financial relationship
83	2008	1991, 1995, 2002, 2004, 2009	Randomization was achieved by asking the participants to choose any number between 1 and 10; even and odd numbers were assigned to bimatoprost (n=41) and travoprost (n=49) groups, respectively	NR	NR/CT	Yes	No	NR	No
84	2008	1991, 1995, 2002, 2004, 2009	Patients were randomized in a ratio of 2:1:1 to the FC (q.d., mornings), BIM 0.03% (q.d., evenings), or TIM 0.5% (b.i.d.) using a computer- generated randomization list (PROC PLAN, SAS Version 8.2, Cary, NC).	NR	NR/CT	NR/CT	Yes	Yes	Yes
85	2008	1991, 1995, 2002, 2004, 2009	NR	White plastic dropper bottles, each labeled with a unique patient number	Yes	NR/CT	Yes	Yes	Yes
86	2008	1991, 1995, 2002, 2004, 2009	NR	NR	Yes	NR/CT	Yes	Yes	Yes
87	2008	1991, 1995, 2002, 2004, 2009	A list of random numbers	Standard containers were used and they were concealed with a study-specific cover and all kept in a standard opaque black medicine vial	Yes	NR/CT	Yes	NR	No

Reference	Year	Network meta-analysis time points study included in	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
88	2009	1991, 1995, 2002, 2004, 2009	Randomization lists were used to preallocate treatment kits to each patient number by personnel not involved with the management of the study.	Randomization lists were used to preallocate treatment kits to each patient number by personnel not involved with the management of the study.	No	No	No	Yes	No
89	2009	1991, 1995, 2002, 2004, 2009	Allocation was based on computer-generated random numbers and was concealed by using sequentially numbered opaque sealed envelopes.	Allocation was based on computer-generated random numbers and was concealed by using sequentially numbered opaque sealed envelopes.	NR/CT	NR/CT	No	NR	Reported none of the authors has any financial relationship
90	2009	1991, 1995, 2002, 2004, 2009	Fifty opaque envelopes containing random numbers (drugs in code forms), generated with the help of table of randomization, were prepared in advance by an investigator who was not related to the study. Whenever, a study participant was found to be eligible, an envelope was opened by another person in the department and the patient was put on the allocation plan as found inside the envelope in coded form.	Fifty opaque envelopes containing random numbers (drugs in code forms), generated with the help of table of randomization, were prepared in advance by an investigator who was not related to the study. Whenever, a study participant was found to be eligible, an envelope was opened by another person in the department and the patient was put on the allocation plan as found inside the envelope in coded form.	Yes	No	No	NR	No
91	2009	1991, 1995, 2002, 2004, 2009	NR	NR	NR/CT	NR/CT	No	NR	No
92	2010	1991, 1995, 2002, 2004, 2009, 2014	A randomization schedule, balanced for ethnicity and drug assignment, was produced for each participating site by the biostatistician.	NR	No	Yes	No	No	No
93	2010	1991, 1995, 2002, 2004, 2009, 2014	The randomization sequence was computer-generated.	the randomization code was retained by the study sponsor and made available to the investigators only after the study had ended.	Yes	No	Yes	Yes	Yes
94	2010	1991, 1995, 2002, 2004, 2009, 2014	Randomization codes were generated by Pfizer according to standard operating procedures and were kept at Global Pharmacy Operations (New York, New York).	NR	NR/CT	Yes	No	Yes	Yes
95	2010	1991, 1995, 2002, 2004, 2009, 2014	The randomisation code was computer-generated.	NR	No	NR/CT	Yes	Yes	Yes
96	2010	1991, 1995, 2002, 2004, 2009, 2014	NR	NR	NR/CT	NR/CT	No	No	Reported none of the authors has any financial relationship
97	2010	1991, 1995, 2002, 2004, 2009, 2014	Patients were randomized using Proc Plan, SAS for Windows (version 8.2, SAS Institute Inc., Cary, NC).	NR	Yes	NR/CT	Yes	Yes	Yes

Reference	Year	Network meta-analysis time points study included in	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
98	2011	1991, 1995, 2002, 2004, 2009, 2014	NR	NR	No	No	No	No	No
99	2011	1991, 1995, 2002, 2004, 2009, 2014	NR	NR	No	No	Yes	NR	No
100	2012	1991, 1995, 2002, 2004, 2009, 2014	Randomization was performed by Ms. Takako Komiya... in research center, after confirming identical appearance of both treatments.	Randomization was performed by Ms. Takako Komiya... in research center, after confirming identical appearance of both treatments.	NR/CT	NR/CT	Yes	Yes	Reported none of the authors has any financial relationship
101	2012	1991, 1995, 2002, 2004, 2009, 2014	Patients were assigned to treatment using a computer-generated randomized allocation schedule prepared by a statistician at Merck	Personnel at each study site used an interactive voice response system to determine which masked treatment containers should be given to which patient.	Yes	Yes	No	Yes	Yes
102	2013	1991, 1995, 2002, 2004, 2009, 2014	NR	NR	No	NR/CT	Yes	Yes	Yes
103	2013	1991, 1995, 2002, 2004, 2009, 2014	NR	NR	No	No	No	NR	Yes
104	2013	1991, 1995, 2002, 2004, 2009, 2014	A list of sequential patient numbers was generated by a member of the sponsor programming group (SAS Institute) not involved in the conduct of the study.	A list of sequential patient numbers was generated by a member of the sponsor programming group (SAS Institute) not involved in the conduct of the study. Study medications were provided in identical bottles. Staff members who provided the study medications to patients did not discuss those medications with other site personnel.	Yes	NR/CT	No	Yes	Yes
105	2013	1991, 1995, 2002, 2004, 2009, 2014	NR	NR	Yes	NR/CT	Yes	Yes	Yes

IOP: Intraocular pressure
NR: Not reported
CT: Can't tell

Color coding:

Green - low risk of bias
Yellow - unclear risk of bias
Pink - high risk of bias

Appendix V. Pair-wise meta-analysis

App V. Table 1. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for drugs in studies published by 1991

		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	Mean difference[a]	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Direct comparisons							
Placebo vs.							
	Brimonidine	-	-	-	-	-	-
	Betaxolol	1	-3.90	-5.29	-2.52	NA	NA
	Levobunolol	1	-6.98	-9.12	-4.84	NA	NA
	Timolol	3	-3.52	-4.65	-2.39	0.45	45%
	Brinzolamide	-	-	-	-	-	-
	Dorzolamide	-	-	-	-	-	-
	Bimatoprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
Apraclonidine vs							
	Timolol	-	-	-	-	-	-
Brimonidine vs							
	Betaxolol	-	-	-	-	-	-
	Timolol	-	-	-	-	-	-
	Brinzolamide	-	-	-	-	-	-
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
Betaxolol vs							
	Levobunolol	1	-2.37	-3.85	-0.90	0.00	0%
	Timolol	4	-1.39	-2.19	-0.58	NA	NA
	Dorzolamide	-	-	-	-	-	-
	Latanoprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
Carteolol vs							
	Levobunolol	-	-	-	-	-	-
	Timolol	-	-	-	-	-	-
Levobunolol vs							
	Timolol	8	0.01	-0.70	0.71	0.31	32%
Timolol vs							
	Brinzolamide	-	-	-	-	-	-
	Dorzolamide	-	-	-	-	-	-
	Bimatoprost	-	-	-	-	-	-
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
	Tafluprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
Brinzolamide vs							
	Dorzolamide	-	-	-	-	-	-
Dorzolamide vs							
	Latanoprost	-	-	-	-	-	-
Bimatoprost vs							
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
Latanoprost vs							
	Travoprost	-	-	-	-	-	-
	Tafluprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-

App V. Table 3. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for drugs in studies published by 2002

		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	Mean difference[a]	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Direct comparisons							
Placebo vs.							
	Brimonidine	1	-2.3	-3.99	-0.61	NA	NA
	Betaxolol	1	-3.9	-5.29	-2.52	NA	NA
	Levobunolol	2	-7.52	-8.53	-6.50	0.00	0%
	Timolol	4	-3.91	-5.12	-2.69	0.85	57%
	Brinzolamide	1	-2.10	-3.44	-0.76	NA	NA
	Dorzolamide	3	-2.59	-3.67	-1.51	0.00	0%
	Bimatoprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
Apraclonidine vs							
	Timolol	2	-0.84	-3.75	2.08	3.73	84%
Brimonidine vs							
	Betaxolol	1	1.94	0.84	3.04	NA	NA
	Timolol	2	0.69	0.28	1.10	0.00	0%
	Brinzolamide	-	-	-	-	-	-
	Latanoprost	3	-1.04	-2.22	0.14	0.83	77%
	Travoprost	-	-	-	-	-	-
Betaxolol vs							
	Levobunolol	1	-2.37	-3.85	-0.90	NA	NA
	Timolol	7	-1.29	-1.71	-0.87	0.00	0%
	Dorzolamide	2	-0.30	-0.96	0.36	0.00	0%
	Latanoprost	-	-	-	-	-	-
	Unoprostone	1	0.6	0.09	1.11	NA	NA
Carteolol vs							
	Levobunolol	1	-2.90	-4.59	-1.22	NA	NA
	Timolol	4	0.03	-0.61	0.68	0.11	24%
Levobunolol vs							
	Timolol	10	-0.03	-0.48	0.43	0.06	12%
Timolol vs							
	Brinzolamide	1	0.90	-0.17	1.97	NA	NA
	Dorzolamide	5	0.76	0.13	1.39	0.24	47%
	Bimatoprost	-	-	-	-	-	-
	Latanoprost	10	-1.35	-1.96	-0.74	0.56	66%
	Travoprost	2	-2.04	-4.19	0.11	2.14	88%
	Tafluprost	-	-	-	-	-	-
	Unoprostone	2	0.94	-0.43	2.31	0.85	87%
Brinzolamide vs							
	Dorzolamide	2	-0.58	-1.15	0.00	0.00	0%
Dorzolamide vs							
	Latanoprost	1	-2.90	-3.7	-2.10	NA	NA
Bimatoprost vs							
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
Latanoprost vs							
	Travoprost	1	-1.40	-2.4	-0.40	NA	NA
	Tafluprost	-	-	-	-	-	-
	Unoprostone	6	3.07	2.51	3.63	0.01	2%

App V. Table 2. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for drugs in studies published by 1995

		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	Mean difference*	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Direct comparisons							
Placebo vs.							
	Brimonidine	-	-	-	-	-	-
	Betaxolol	1	-3.90	-5.29	-2.52	NA	NA
	Levobunolol	2	-7.52	-8.53	-6.50	0.00	0%
	Timolol	4	-3.91	-5.12	-2.69	0.85	57%
	Brinzolamide	-	-	-	-	-	-
	Dorzolamide	1	-2.90	-5.23	-0.57	NA	NA
	Bimatoprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
Apraclonidine vs							
	Timolol	1	0.80	-1.31	2.91	NA	NA
Brimonidine vs							
	Betaxolol	-	-	-	-	-	-
	Timolol	-	-	-	-	-	-
	Brinzolamide	-	-	-	-	-	-
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
Betaxolol vs							
	Levobunolol	1	-2.37	-3.85	-0.90	NA	NA
	Timolol	5	-1.52	-2.18	-0.86	0.00	0%
	Dorzolamide	1	-0.60	-1.70	0.50	NA	NA
	Latanoprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
Carteolol vs							
	Levobunolol	1	-2.90	-4.59	-1.22	NA	NA
	Timolol	1	-0.70	-2.26	0.86	NA	NA
Levobunolol vs							
	Timolol	9	-0.03	-0.60	0.55	0.16	22%
Timolol vs							
	Brinzolamide	-	-	-	-	-	-
	Dorzolamide	2	0.65	-0.43	1.73	0.41	68%
	Bimatoprost	-	-	-	-	-	-
	Latanoprost	1	-0.90	-1.73	-0.07	NA	NA
	Travoprost	-	-	-	-	-	-
	Tafluprost	-	-	-	-	-	-
	Unoprostone	1	0.20	-0.63	1.03	NA	NA
Brinzolamide vs							
	Dorzolamide	-	-	-	-	-	-
Dorzolamide vs							
	Latanoprost	-	-	-	-	-	-
Bimatoprost vs							
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
Latanoprost vs							
	Travoprost	-	-	-	-	-	-
	Tafluprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-

App V. Table 4. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for drugs in studies published by 2004

		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	Mean difference[a]	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Direct comparisons							
Placebo vs.							
	Brimonidine	1	-2.3	-3.99	-0.61	NA	NA
	Betaxolol	2	-2.9	-4.65	-1.15	1.30	81%
	Levobunolol	2	-7.52	-8.53	-6.50	0.00	0%
	Timolol	4	-3.91	-5.12	-2.69	0.85	57%
	Brinzolamide	1	-2.1	-3.44	-0.76	NA	NA
	Dorzolamide	3	-2.59	-3.67	-1.51	0.00	0%
	Bimatoprost	-	-			-	-
	Unoprostone	1	-0.2	-1.56	1.16	NA	NA
Apraclonidine vs							
	Timolol	2	-0.84	-3.75	2.08	3.73	84%
Brimonidine vs							
	Betaxolol	1	1.94	0.84	3.04	NA	NA
	Timolol	2	0.69	0.28	1.10	0.00	0%
	Brinzolamide	-	-	-	-	-	-
	Latanoprost	4	-1.04	-1.86	-0.22	0.46	67%
	Travoprost	-	-	-	-	-	-
Betaxolol vs							
	Levobunolol	1	-2.37	-3.85	-0.90	NA	NA
	Timolol	7	-1.29	-1.71	-0.87	0.00	0%
	Dorzolamide	2	-0.3	-0.96	0.36	0.00	0%
	Latanoprost	1	-0.2	-2.20	1.80	NA	NA
	Unoprostone	1	0.6	0.09	1.11	NA	NA
Carteolol vs							
	Levobunolol	1	-2.9	-4.59	-1.22	NA	NA
	Timolol	4	0.03	-0.61	0.68	0.11	24%
Levobunolol vs							
	Timolol	10	-0.03	-0.48	0.43	0.06	12%
Timolol vs							
	Brinzolamide	2	0.67	-0.51	1.85	0.12	7%
	Dorzolamide	5	0.76	0.13	1.39	0.24	47%
	Bimatoprost	2	-2.17	-2.89	-1.45	0.00	0%
	Latanoprost	12	-1.4	-1.91	-0.89	0.44	64%
	Travoprost	2	-2.04	-4.19	0.11	2.14	88%
	Tafluprost	-	-	-	-	-	-
	Unoprostone	2	-0.58	-1.15	0.00	0.85	87%
Brinzolamide vs							
	Dorzolamide	2	-0.58	-1.15	0.00	0.00	0%
Dorzolamide vs							
	Latanoprost	1	-2.9	-3.70	-2.10	NA	NA
Bimatoprost vs							
	Latanoprost	2	0.59	-0.36	1.54	0.17	28%
	Travoprost	1	0.6	-0.16	1.36	NA	NA
Latanoprost vs							
	Travoprost	3	-0.35	-1.52	0.83	0.76	73%
	Tafluprost	-	-	-	-	-	-
	Unoprostone	6	3.07	2.51	3.63	0.01	2%

App V. Table 5. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for drugs in studies published by 2009

		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	Mean difference*	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Direct comparisons							
Placebo vs.							
	Brimonidine	1	-2.30	-3.99	-0.61	NA	NA
	Betaxolol	2	-2.90	-4.65	-1.15	1.30	81%
	Levobunolol	2	-7.52	-8.53	-6.50	0.00	0%
	Timolol	4	-3.91	-5.12	-2.69	0.85	57%
	Brinzolamide	1	-2.10	-3.44	-0.76	NA	NA
	Dorzolamide	4	-1.91	-2.92	-0.90	0.51	51%
	Bimatoprost	-	-	-	-	-	-
	Unoprostone	1	3.07	2.51	3.63	NA	NA
Apraclonidine vs							
	Timolol	2	-0.84	-3.75	2.08	3.73	84%
Brimonidine vs							
	Betaxolol	1	1.94	0.84	3.04	NA	NA
	Timolol	3	0.66	0.25	1.06	0.00	0%
	Brinzolamide	-	-	-	-	-	-
	Latanoprost	5	-1.36	-2.21	-0.50	0.73	78%
	Travoprost	1	-1.20	-3.77	1.37	NA	NA
Betaxolol vs							
	Levobunolol	2	-4.73	-10.01	0.55	12.25	83%
	Timolol	8	-1.58	-2.29	-0.87	0.43	48%
	Dorzolamide	2	-0.30	-0.96	0.36	0.00	0%
	Latanoprost	2	-1.06	-2.62	0.51	0.33	25%
	Unoprostone	1	0.60	0.09	1.11	NA	NA
Carteolol vs							
	Levobunolol	1	-2.90	-4.59	-1.22	NA	NA
	Timolol	4	0.03	-0.61	0.68	0.11	24%
Levobunolol vs							
	Timolol	11	-0.03	-0.44	0.39	0.01	3%
Timolol vs							
	Brinzolamide	3	1.10	0.50	1.70	0.00	0%
	Dorzolamide	5	0.76	0.13	1.39	0.24	47%
	Bimatoprost	5	-2.07	-2.64	-1.49	0.15	35%
	Latanoprost	12	-1.40	-1.91	-0.89	0.44	64%
	Travoprost	5	-1.22	-2.20	-0.24	0.79	67%
	Tafluprost	-	-	-	-	-	-
	Unoprostone	2	0.94	-0.43	2.31	0.85	87%
Brinzolamide vs							
	Dorzolamide	2	-0.58	-1.15	0.00	0.00	0%
Dorzolamide vs							
	Latanoprost	1	-2.90	-3.70	-2.10	NA	NA
Bimatoprost vs							
	Latanoprost	5	0.98	0.02	1.93	0.90	80%
	Travoprost	4	0.62	-0.80	2.05	1.82	87%
Latanoprost vs							
	Travoprost	5	-0.32	-1.01	0.37	0.30	50%
	Tafluprost	-	-	-	-	-	-
	Unoprostone	6	3.07	2.51	3.63	0.01	2%

App V. Table 6. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for drugs in studies published by 2014

		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	Mean difference*	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Direct comparisons							
Placebo vs.							
	Brimonidine	1	-2.30	-3.99	-0.61	NA	NA
	Betaxolol	2	-2.90	-4.65	-1.15	1.30	81%
	Levobunolol	2	-7.52	-8.53	-6.50	NA	NA
	Timolol	4	-3.91	-5.12	-2.69	0.85	57%
	Brinzolamide	2	-2.17	-3.23	-1.10	0.00	0%
	Dorzolamide	4	-1.91	-2.92	-0.90	0.51	51%
	Bimatoprost	1	-4.60	-5.60	-3.60	NA	NA
	Unoprostone	1	-0.20	-1.56	1.16	NA	NA
Apraclonidine vs							
	Timolol	2	-0.84	-3.75	2.08	3.73	84%
Brimonidine vs							
	Betaxolol	1	1.94	0.84	3.04	NA	NA
	Timolol	4	0.17	-0.70	1.03	0.55	81%
	Brinzolamide	2	1.01	0.50	1.53	0.00	0%
	Latanoprost	5	-1.36	-2.21	-0.50	0.73	78%
	Travoprost	1	-1.20	-3.77	1.37	NA	NA
Betaxolol vs							
	Levobunolol	2	-4.73	-10.01	0.55	12.25	83%
	Timolol	8	-1.58	-2.29	-0.87	0.43	48%
	Dorzolamide	2	-0.30	-0.96	0.36	0.00	0%
	Latanoprost	2	-1.06	-2.62	0.51	0.33	25%
	Unoprostone	1	0.60	0.09	1.11	NA	NA
Carteolol vs							
	Levobunolol	1	-2.90	-4.59	-1.22	NA	NA
	Timolol	4	0.03	-0.61	0.68	0.11	24%
Levobunolol vs							
	Timolol	11	-0.03	-0.44	0.39	0.01	3%
Timolol vs							
	Brinzolamide	3	1.10	0.50	1.70	0.00	0%
	Dorzolamide	5	0.76	0.13	1.39	0.24	47%
	Bimatoprost	5	-2.07	-2.64	-1.49	0.15	35%
	Latanoprost	14	-1.32	-1.77	-0.88	0.40	64%
	Travoprost	5	-1.22	-2.20	-0.24	0.79	67%
	Tafluprost	1	-0.30	-0.72	0.12	NA	NA
	Unoprostone	2	0.94	-0.43	2.31	0.85	87%
Brinzolamide vs							
	Dorzolamide	2	-0.58	-1.15	0.00	0.00	0%
Dorzolamide vs							
	Latanoprost	1	-2.90	-3.70	-2.10	NA	NA
Bimatoprost vs							
	Latanoprost	6	0.87	0.01	1.73	0.82	76%
	Travoprost	8	0.59	-0.13	1.30	0.73	74%
Latanoprost vs							
	Travoprost	7	-0.22	-0.86	0.41	0.33	48%
	Tafluprost	1	-0.90	-3.40	1.60	NA	NA
	Unoprostone	6	3.07	2.51	3.63	0.01	2%

App V. Table 7. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for classes in studies published by 1991

		Comparison-specific heterogeneity					
Column 1 Direct comparisons	Column 2	Num. of studies	Mean difference[a]	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs							
	Alpha agonists	-	-	-	-	-	-
	Beta blockers	5	4.11	-5.31	-2.91	1.22	67%
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	-	-	-	-	-	-
Alpha agonists vs							
	Beta blockers	-	-	-	-	-	-
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	-	-	-	-	-	-
Beta Blockers vs							
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	-	-	-	-	-	-
Carbonic anhydrase inhibitors vs							
	Prostaglandins	-	-	-	-	-	-

App V. Table 8. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for classes in studies published by 1995

		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	Mean difference[a]	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Direct comparisons							
Placebo vs							
	Alpha agonists	-	-	-	-	-	-
	Beta blockers	7	-4.91	-6.43	-3.38	3.53	86%
	Carbonic anhydrase inhibitors	1	-2.90	-5.23	-0.57	NA	NA
	Prostaglandins	-	-	-	-	-	-
Alpha agonists vs							
	Beta blockers	1	0.80	-1.31	2.91	NA	NA
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	-	-	-	-	-	-
Beta Blockers vs							
	Carbonic anhydrase inhibitors	3	0.27	-0.73	1.28	0.56	71%
	Prostaglandins	2	-0.35	-1.43	0.73	0.43	70%
Carbonic anhydrase inhibitors vs							
	Prostaglandins	-	-	-	-	-	-

App V. Table 8. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for classes in studies published by 2002

		Comparison-specific heterogeneity					
Column 1 Direct comparisons	Column 2	Num. of studies	Mean difference[a]	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs							
	Alpha agonists	1	-2.3	-3.99	-0.61	NA	NA
	Beta blockers	7	-4.91	-6.43	-3.38	3.53	86%
	Carbonic anhydrase inhibitors	4	-2.4	-3.24	-1.55	0.00	0%
	Prostaglandins	-	-	-	-	-	-
Alpha agonists vs							
	Beta blockers	5	0.39	-0.73	1.51	1.32	87%
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	3	-1.04	-2.22	0.14	0.83	77%
Beta Blockers vs							
	Carbonic anhydrase inhibitors	8	0.49	-0.04	1.02	0.31	54%
	Prostaglandins	15	-1.02	-1.76	-0.27	1.78	90%
Carbonic anhydrase inhibitors vs							
	Prostaglandins	1	-2.9	-3.7	-2.10	NA	NA

App V. Table 9. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for classes in studies published by 2004

		Comparison-specific heterogeneity					
Column 1 Direct comparisons	Column 2	Num. of studies	Mean difference[a]	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs							
	Alpha agonists	1	-2.3	-3.99	-0.61	NA	NA
	Beta blockers	8	-4.52	-6.11	-2.93	4.66	91%
	Carbonic anhydrase inhibitors	4	-2.4	-3.24	-1.55	0.00	0%
	Prostaglandins	1	-0.2	-1.56	1.16	NA	NA
Alpha agonists vs							
	Beta blockers	5	0.39	-0.73	1.51	1.32	87%
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	4	-1.04	-1.86	-0.22	0.46	67%
Beta Blockers vs							
	Carbonic anhydrase inhibitors	9	0.46	-0.06	0.97	0.29	50%
	Prostaglandins	20	-1.19	-1.84	-0.54	1.78	90%
Carbonic anhydrase inhibitors vs							
	Prostaglandins	1	-2.9	-3.70	-2.10	NA	NA

App V. Table 10. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for classes in studies published by 2009

		Comparison-specific heterogeneity					
Column 1 Direct comparisons	Column 2	Num. of studies	Mean difference[a]	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs							
	Alpha agonists	1	-2.30	-3.99	-0.61	NA	NA
	Beta blockers	8	-4.52	-6.11	-2.93	4.66	91%
	Carbonic anhydrase inhibitors	5	-1.89	-2.66	-1.12	0.31	43%
	Prostaglandins	1	-0.20	-1.56	1.16	NA	NA
Alpha agonists vs							
	Beta blockers	6	0.29	-0.76	1.34	1.26	84%
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	6	-1.35	-2.14	-0.55	0.65	72%
Beta Blockers vs							
	Carbonic anhydrase inhibitors	10	0.57	0.08	1.06	0.33	55%
	Prostaglandins	27	-1.25	-1.79	-0.72	1.58	88%
Carbonic anhydrase inhibitors vs							
	Prostaglandins	1	-2.90	-3.70	-2.10	NA	NA

App V. Table 11. Summary estimates for intraocular pressure at 3 months derived from pair-wise meta-analysis for classes in studies published by 2014

		Comparison-specific heterogeneity					
Column 1 Direct comparisons	Column 2	Num. of studies	Mean difference[a]	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs							
	Alpha agonists	1	-2.30	-3.99	-0.61	NA	NA
	Beta blockers	8	-4.52	-6.11	-2.93	4.66	91%
	Carbonic anhydrase inhibitors	6	-1.90	-2.57	-1.23	0.24	36%
	Prostaglandins	2	-2.43	-6.74	1.89	9.31	96%
Alpha agonists vs							
	Beta blockers	7	0.12	-0.81	1.05	1.18	86%
	Carbonic anhydrase inhibitors	2	1.01	0.50	1.53	0.00	0%
	Prostaglandins	6	-1.35	-2.14	-0.55	0.65	72%
Beta Blockers vs							
	Carbonic anhydrase inhibitors	10	0.57	0.08	1.06	0.33	55%
	Prostaglandins	30	-1.18	-1.64	-0.72	1.26	87%
Carbonic anhydrase inhibitors vs							
	Prostaglandins	1	-2.90	-3.70	-2.10	NA	NA

[a] Mean difference is calculated using the intraocular pressure of the treatment in column 2 - column 1

Mean difference > 0 favors the drug in column 1

Mean difference < 0 favors the drug in column 2

Color coding:

Grey	Placebo/vehicle/no treatment
Orange	Alpha-2 adrenergic agonist
Green	Beta-blocker
Red	Carbonic anhydrase inhibitor
Blue	Prostaglandin analog

Curriculum Vitae

Benjamin Rouse

7926 Starburst Drive, Pikesville, MD 21208

(410) 653-3412
brouse1@jhu.edu

EDUCATION

Master of Health Sciences (MHS) in Epidemiology Expected May 2015
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Concentration: Clinical Trials and Evidence Synthesis
G.P.A.: 3.93/4.00

University of Illinois at Chicago College of Pharmacy, Chicago, IL
Graduate-level coursework in Medicinal Chemistry and Pharmacognosy
G.P.A.: 4.00/4.00

Bachelor of Liberal Arts & Science May 2014
Harriet L. Wilkes Honors College at Florida Atlantic University, Jupiter, FL
Concentration: Chemistry
Summa cum Laude
G.P.A.: 3.917/4.000
Thesis: Presumptive and Confirmatory Tests for Illicit Drug Analogs

June 2007
Shoshana S. Cardin Jewish Community High School, Baltimore, MD
G.P.A.: 3.83/4.00

RESEARCH AND WORK EXPERIENCE

Research Assistant - Johns Hopkins University February 2014-present

- Contribute to systematic reviews and methodology research for the Cochrane Eyes and Vision Group
- Direct screening of literature to identify studies relevant for reviews
- Extraction of relevant methodological details and results of studies for reviews

Teaching Assistant - University of Illinois at Chicago August 2011-May 2013

- Hold office hours to answer students' questions about the course material
- Proctor and grade course exams

Research Assistant - University of Illinois at Chicago August 2011-December 2012

- Utilize various chromatography techniques for the isolation and purification of natural products from plants and bacteria
- Structural elucidation of natural products with mass spectrometry and nuclear magnetic resonance

BioTools Intern - Jupiter, FL August 2010-December 2010

- Review literature on using infrared spectroscopy for analyzing three dimensional structure of proteins
- Work with the PROTA Fourier Transform-Infrared Protein Analyzer for determining secondary structure of proteins

PUBLICATIONS AND PRESENTATIONS

Journal Articles

- **Rouse, Benjamin**; Schneider, Rebecca; Smith, Eugene. Presumptive and Confirmatory Tests using Analogs of Illicit Drugs: An Undergraduate Instrumental Methods Exercise. *Journal of Chemical Education*. 2014; 19:70-72.

Poster Presentations

- University of Illinois at Chicago - March 9, 2012
  Chicago, Illinois
  College of Pharmacy Research Day
  Bioassay-Guided Fractionation and Dereplication of Anti-Cancer Compound from Nostoc sp. (UIC 10366)
  Rouse, B, Kang, HS, Zinkus, J, Swanson, S, Orjala, J

- Harriet L. Wilkes Honors College - April 15, 2011
  Jupiter, FL
  9th Annual Symposium for Research and Creative Projects
  Presumptive and Confirmatory Tests for Illicit Drug Analogs
  Rouse, B, Smith, E

- University of Maryland at Baltimore County - October 30, 2010
  Baltimore, Maryland
  13th Annual Undergraduate Research Symposium in the Chemical and Biological Sciences
  Qualitative Analysis of Amphetamine and GHB Analogs
  Rouse, B, Smith, E

PROFESSIONAL DEVELOPMENT

Computer skills: Microsoft Office Suite (including Word, Excel, and PowerPoint)
Statistical software: Stata, SAS, and R Packages